A Textbook of

MEDICINE

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Preface to the Tenth Edition

THE EDITORS are pleased to present to students and physicians the Tenth Edition of this textbook. This edition reflects the many strides which have been made in Medicine during the past four years. As in earlier editions it has been attempted as far as possible to incorporate discussions of pathological physiology and disease mechanisms into the total discussion of disease. When this has not been feasible, sections on metabolic and physiological processes in health and disease have been placed in close proximity to the clinical description of the diseases to which they are particularly relevant because in terms of biological processes fragmentation of the discussion of disease is artificial. For example, to achieve this end a section by Dr. Joseph W. Jailer on the physiology and metabolism of the steroids has been introduced preceding the description of diseases of the adrenal and sex glands.

The Tenth Edition contains the following articles on subjects which have not been covered in previous editions:

Adenoviral Infections	Dr. Yale Kneeland
Pharyngoconjunctival Fever	Dr. Yale Kneeland
Cytomegalic Inclusion Disease	Dr. Edwin D. Kilbourne
ECHO Viral Infections	Dr. Robert H. Huebner
Granuloma Inguinale	Dr. Walsh McDermott
Erysipeloid of Rosenbach	Dr. Karl F. Meyer
Diseases Due to Atypical Acid Fast Bacilli	Dr. Burns Amberson
Tropical Ulcer	Dr. Thomas B. Turner
Heterodera Radicicola	Dr. Harold W. Brown
Cranial (Temporal) Arteritis	Dr. A. McGehee Harvey
Thrombotic Thrombopenic Purpura	Dr. A. McGehee Harvey
High Altitude Sickness	Dr. Robert C. Darling
Silo Filler's Disease	Dr. William J. McConnell
Salicylate Poisoning	Dr. Henry Aranow, Jr.
Metal Fume Fever	Dr. Henry Aranow, Jr.
Pantothenic Acid Deficiency	Dr. Tom D. Spies
Renal Glycosuria	Dr. Alexander B. Gutman
Oxalosis	Dr. Alexander B. Gutman
Aminoacidurias	Dr. Alexander B. Gutman
Renal Hypophosphatemia	Dr. Alexander B. Gutman
Renal Tubular Acidosis	Dr. Alexander B. Gutman
Agammaglobulinemia	Dr. Charles A. Janeway
Carcinoidosis	Dr. Albert Sjoerdsma
Hyponatremia and Hypokalemia	Dr. Robert Berliner
Steroid Physiology and Metabolism	Dr. Joseph W. Jailer
Hyperaldosteronism	Dr. George W. Thorn
Acute Pseudomembranous Enterocolitis	Dr. Walter L. Palmer
Hepatic Coma	Dr. Arthur J. Patek
Cystic Fibrosis of the Pancreas	Dr. Paul H. di Sant'Agnese

Cryoglobulinemia and Macroglobulinemia	Dr Alfred Gellhorn
Myeloproliferative Disorders Including Myeloid Metaplasia	Dr William B Castle
Cervical Spondylosis	Sir Russell Brain
Benign Intracranial Hypertension	Dr Bronson S Ray
Electric Shock Treatment in Psychiatric Therapy	Dr Peter F Regan III
Tietze s Syndrome	Dr Walter Bauer Dr Frederic C Bartter
Marfan s Syndrome	Dr Walter Bauer Dr Frederic C Bartter

Despite the inclusion of this new material there has been no sacrifice of clinical con siderations This has been achieved by uti lizing a new and clearer type which makes possible an increase in the text without an increase in the number of pages

It is with regret that the Editors report the deaths of the following contributors Dr Janet S Baldwin Dr Thomas A C Rennie and Dr Ephraim Shorr The following new contributors have written sections formerly covered by those lost by death or retirement Dr Robert B Aird Dr Henry Aranow Jr Dr Harry L Arnold Dr Richard G Bing Sir Russell Brain Dr Harold W Brown Dr C Lee Buxton Dr Ronald V Christie Dr Alfred Gellhorn Dr Melvin M Grumbach Dr Franz J Ingelfinger Dr Joseph W Jailer Dr Robert A Kehoe Dr Lawrence C Kolb Dr Herbert Koteen Dr Charles A Le Maistre Dr Fletcher H McDowell Dr George A Perera Dr Peter F Regan III Dr Arnold S Relman Dr Lamar Roberts Dr Paul A di Sant Agnese Dr R Walter Schles inger Dr Albert Sjoerdsma Dr John B Stanbury Dr DeWitt Stetten Dr John V Taggart Dr David Weiman Dr Eric Wol laeger and Dr Sam Bernard Wortis

It is axiomatic that however excellent the content of a textbook may be its usefulness to the student can be measured by the com pleteness of its index With this point of view in mind the Editors have laid unusual emphasis upon the preparation of an index which will enhance the value of the book

The Editors wish to direct the attention of the reader to the Foreword by Dr Dana W Atchley The impressive data presented in the subsequent 1600 pages are of limited value in the actual practice of medicine un less they are considered within the frame work of the timeless philosophy expressed in this Foreword which deals with the problems of Patient Physician Communi cation

The Editors extend their sincere thanks to the distinguished contributors who have written for this Tenth Edition Without their full cooperation this textbook would not exist They also wish to express their ap preciation to the officers and staff of the W B Saunders Company for their constant help and advice Grateful acknowledgment is due Mrs Ann Tourtellot for proofreading and editorial work

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A Foreword

PATIENT-PHYSICIAN COMMUNICATION

Osler early in this century quoted Galen as saying He cures most successfully in whom the people have the greatest confidence" This long recognized truth is so important that it would seem appropriate to consider in a brief foreword some of the qualities of the physician as healer that are as essential to his success as is the scientific knowledge he can gain from text book or journal A familiarity with disease patterns and an understanding of their mechanisms are of course essential to the sound practice of medicine but they can be sadly inadequate in the absence of effective communication between doctor and patient This communication must be in both directions as much from the doctor to patient as the reverse and it should be on as many levels as is mutually possible It is not surprising that the increasingly accurate comprehension of disease processes has tended to emphasize the essential individuality of patients in all respects This individuality is particularly evident in the variations of personality and full comprehension of personality is gained only by good communication

A sympathetic and discerning history provides the first and most important step as the patient and doctor come to know each other While the unhurried interviewer listens responsively to the ill person s problems a rapport is established that can soon be turned to an investigation of family marriage work and other environmental factors from which the portrait of a single human being emerges With success this portrait quickly comes to life first as an acquaintance and then as a friend Success is dependent on a convincing expression of real interest and on equally genuine evidence that the doctor cares whether his patient is sick or well happy or unhappy The doctor who must force himself to listen to patients or finds himself indifferent to suffering should transfer to a branch of medicine that does not involve personal relationships with the sick

Communication on the emotional level is therefore a basic necessity for initiating relationships at other levels Warmth and compassion break down the barriers of anxiety and fear that beset the patient coming as a stranger to the doctor barriers that can seriously inhibit the thoroughness of a diagnostic appraisal If a patient feels that his problems are provocative not only of scientific interest but also of a deep concern over his happiness he will be more open in discussing his life and his deeper feelings and also more cooperative in accepting unpleasant diagnostic and therapeutic procedures A good emotional rapport between the doctor and his patient improves his efficiency as a healer and indeed makes the whole process more pleasant The physician should be careful not to give too much of himself emotionally or he will be in danger of losing his objectivity and perhaps his poise He must not dispel the patient s anxiety by taking it on to himself The devotion to which

at least minimal unhappiness and situations can arise wherein this goal might be defeated by austere frankness Sophisticated and compassionate physicians are faced with the question whether they may claim for themselves the serious authority of deciding to protect a patient from devastating truth Of course mature and intelligent insistence on the complete picture cannot be refused but such a request is rare more often such a demand from the patient is in reality based on an anxious and unconscious search for reassurance It is this latter group that imposes the most difficult responsibility upon the physician he may share it with his colleagues or with the patient s relatives but the ultimate painful decision is his The truth should be adhered to as far as is humanely possible but if the physician should deem it wise to veil the truth the presentation should be so convincing that the dire effects of discovery will never ensue In any event the truth should be tempered with mercy because of the fallibility of prognosis It is difficult to subject any area of human relations to dogmatic ethical codes rigidly imposed and especially is this true in relation to suffering human beings Each case must be handled individually with one guiding principle to provide minimal unhappiness for all concerned and an outlook compatible with living

A most important but rarely mentioned component of doctor patient communication is *humor* A light touch may not be life saving but it can lift many clouds of depression and anxiety It is the best ice breaker for the patient frozen by fear or by the strangeness of medical routines Stilted Pollyanna reassurances are of little value indeed may be harmful but a wry comment on the absurdities of some medical customs can leave a patient smiling and cooperative This level of communication should never be neglected and its constructive value never discounted

When all the gain from good communication has been achieved and all knowledge from textbook and technical studies has been mobilized there is a final step that is no less crucial than are all the others This is the wise and scientific integration of all the varieties of data into the biological portrait of a single human being This is the art of medicine and like all great art it is the skillful and creative application of a scientific discipline to a human problem

DANA W ATCHLEY

the sick person is so vulnerable is easy for the doctor to exploit It can be an effective agent for the enforcing of therapeutic management but it can also cause many painful complications if it is not employed wisely and unselfishly

Communication on a cultural level is enriching to the patient-doctor relationship This can be based on a mutual interest in the arts literature history or even politics Or it can be an interchange between two individuals who have experienced different environments Learning about other strata of society or different national and ethnic backgrounds is rewarding to the doctor and is of practical value when he plans his patient s management The facts that appear at this level of contact are probably more nearly accurate than any the physician can find elsewhere The medical profession is fortunate in being able thus to tap original sources of information it is one of its greatest rewards And the patient also profits as he is exposed to the disinterested comments of a wise and cultivated scientist Here again the doctor and patient give of themselves in happy interchange

Although confidence may be initiated on the emotional level a firm foundation requires *communication on an intellectual level* The first step at this level is a careful explanation of the nature and purpose of the physical appraisal It is obviously necessary for the doctor to be scientifically trained and for the patient to have a certain degree of intelligence and education Both of these conditions are increasingly fulfilled in our present society Only the uninformed are benefited by the secretive authoritarianism used in previous centuries to mask ignorance Although some men *have a greater gift of exposition than* others and patients vary in their receptivity it is a rare situation in which the disease mechanisms and their clinical setting cannot be so adequately explained to the patient that his management can proceed from understanding rather than blind faith More and more the psychic and somatic individuality of human beings requires that the experimental method be the basis of their treatment Patients therefore must learn the elements of this method and carry out much of the experimentation under their own supervision Without good expository communication such programs will inevitably fail Unfortunately many such failures derive from the doctor s own lack of understanding or worse his lack of interest

The level of *mutual integrity in communication* is so vital to good doctor patient relationships that it may almost be given top priority There is no excuse for the physician who fails here but deception on the part of the patient is often the manifestation of a neurosis Such dishonesty is clinical not ethical The basic integrity of the physician in relation to a patient deserves attentive consideration and has many complex implications The doctor must be honest within himself he must face his motivations clearly and candidly He must not over restrict his patient to protect himself His prognoses must not be hedged out of fear for his own reputation for accuracy He must have the honesty and courage to admit his mistakes to patients when indicated but always to himself and his colleagues

It is essential that the patient trust his doctor he must know that his confidences are never broken However the impingement of simple ethics on the physician s sense of responsibility to his patient creates a number of subtle conflicts between duty to code and duty to patient Much has been said with considerable heat on the question "Shall the patient be told the strict truth? This problem has two phases on one hand the revealing of facts that are clearly not disturbing to the patient that are indeed essential to intelligent cooperation *and on the other hand the imparting* of information of such dread import that hope and happiness are forthwith destroyed

The first phase needs little discussion It *should be accomplished* with calm exposition rather than dramatic declarations If the studies have revealed no clear answer the doctor s "I don t know should never seem to indicate cessation of interest It should have continuity inherent in its mood

The transmission of bad news may require only optimistic slanting without actual falsity there need be no trauma here *to the physician s values The real problem* lies in the area where evasion might be deemed advisable The ultimate goal of medicine is conceded to be happiness or

The Infectious Diseases

VIRAL DISEASES

Introduction

Infectious diseases are usually classified according to the kind of infectious agent which induces them The clinical manifestations of these various diseases differ widely and the agents which cause them are also dissimilar The following groups of infectious agents are recognized protozoa fungi bacteria rickettsiae and viruses These causal agents have a single property in common all are capable of multiplication in an appropriate environment The degree of their structural differentiation as well as their size decreases from the protozoa to the viruses in the order given viruses are the smallest of known agents capable of inducing infectious disease One or another of the pathogenic agents included among the viruses is either known or believed to be the primary cause of each of some fifty different infectious diseases of man These are

Adenovirus infections
B virus infection
Cat scratch fever
Colorado tick fever
Common cold
Coxsackie and ECHO virus infections
Dengue
Durand s disease
Encephalitis lethargica
Encephalitis Japanese type B
Encephalitis Murray Valley type
Encephalitis Russian Far East type
Encephalitis St Louis type
Encephalitis West Nile type
Encephalomyocarditis
Epidemic pleurodynia
Epidemic viral gastroenteritis
Equine encephalomyelitis Eastern
Equine encephalomyelitis Venezuelan
Equine encephalomyelitis Western
Equine infectious anemia
Exanthem subitum
Foot and mouth disease
Hemorrhagic meningo-encephalitis
Herp s simplex
Herpes zoster
Inclusion conjunctivitis
Infectious hepatitis and serum hepatitis
Infectious mononucleosis
Infectious polyneuritis
Influenza (A B and C)
Kerato-conjunctivitis
Louping ill
Lymphocytic choriomeningitis
Lymphogranuloma venereum
Measles
Molluscum contagiosum
Mumps
Newcastle disease
Phlebotomus fever
Poliomyelitis
Primary atypical pneumonia
Psittacosis
Rabies
Rift Valley fever
Rubella
Salivary gland virus infection
Smallpox
Trachoma
Vaccinia
Varicella
Warts
Yellow fever

The nature of viruses is not yet definitely known but certain facts appear well established Viruses are particulate entities which can be visualized by sufficiently powerful instruments *e g* the electron microscope Multiplication of viruses occurs under suitable conditions in the presence of living cells but in the absence of living cells no virus has as yet shown any evidence of multiplication Discontinuous variation has been observed with certain ones

widespread of all infections and is a leading cause of minor incapacitation and absence from work It is not an entity but rather a diagnostic residuum after the exclusion of disease caused by such recognizable agents as the influenza viruses or streptococci

Extensive studies in the U S Army during World War II by the Commission on Acute Respiratory Disease resulted in the separation on clinical grounds of two conditions designated "Acute Undifferentiated Respiratory Disease (ARD) and "Nonstreptococcal Exudative Pharyngitis These two together with certain other clinical conditions have recently been shown to be caused by infection with a newly identified group of viruses called "adenoviruses The whole subject of common respiratory disease will be presented under two headings The Common Cold and Adenoviral Infections

THE COMMON COLD
(*Acute Coryza*)

Definition The common cold is an acute inflammation of the upper respiratory tract which is ordinarily communicable and caused by a filterable virus Such terms as "acute rhinitis" pharyngitis and laryngitis have often been used to denote the area chiefly involved

Etiology Kruse in 1914 was the first to adduce evidence of a filterable virus in colds These observations were considerably extended by Dochez and his co workers who repeatedly demonstrated the presence of a filterable agent in acute coryza capable of causing colds when introduced into an anthropoid ape or a susceptible human volunteer and succeeded in cultivating it in tissue culture medium and the developing chick embryo These filterable agents were obtained early in the course of the coryzal type of cold and the experimental disease had a short incubation period of twelve to forty-eight hours The cultivation of the cold virus has been confirmed by certain writers but others have failed to do so it would appear from the inconstancy of the results that the agent is not readily adapted to the chick embryo The work on filtrate colds however has been abundantly repeated Moreover there is very recent preliminary evidence that new techniques of virus cultivation may yield positive results There seems little doubt therefore that a filterable virus of the common cold exists and presumably is the causative agent in the great majority of cases notably of the epidemic type A great deal however still remains to be elucidated It is not known how many different cold viruses there are there is no precise information as to how long the virus is carried in the respiratory tract or what the conditions of transmission may be and little knowledge concerning immunity to colds is available Moreover it cannot be said with certainty that under certain conditions the common respiratory pathogenic bacteria do not initiate colds although the evidence is against this possibility Studies of small isolated communities such as those conducted by Paul and Freese in Spitzbergen imply that in the absence of the virus the common cold almost wholly disappears Presumably the residuum of sporadic noncommunicable colds may be due to bacterial infection

In spite of extensive investigation for many decades the exact role of the bacterial inhabitants of the nasopharynx is not clear Most students agree that a considerable part of the so-called basal flora" of the upper respiratory tract consists of non pathogenic and inconsequential agents In this category would be placed the various Neisseriae diphtheroids nonhemolytic streptococci most of the staphylococci and so on On the other hand hemolytic streptococci pneumococci and *Hemophilus influenzae* are proved respiratory pathogens and when they are recovered in considerable numbers from a patient with a cold it is tempting to assume that they are playing a role of some sort Undoubtedly hemolytic streptococci can initiate exudative pharyngitis without any assistance from a filterable virus as evidenced by the food and milk borne outbreaks of this disease Perhaps *H influenzae* can in unusual circumstances do the same sort of thing as in "Woodside throat which was described in the Australian Army at the outbreak of World War II On the other hand any of these organisms may appear in the normal nasopharynx without causing symptoms and the mere recovery of one of them from a case of coryza may be of little significance Most authors tend to designate them as secondary invaders assuming that the cold virus paves the way for their entry into the mucous membranes Yet when effective chemotherapeutic agents have been used in large scale controlled experiments on adults with colds there is little evidence that suppression of the bacterial component alters the average duration of the disease Perhaps the best way to define the activity of the bacteria is in relation to the susceptibility of the population under scrutiny Infants and small children to

Viruses differ widely in size stability and degree of apparent structural differentiation

The smallest viruses (with dimensions of 10 to 28 mμ)—*e g* those responsible for foot and mouth disease and poliomyelitis—are particles only slightly larger than serum globulin molecules and are actually considerably smaller than the hemocyanin molecules of certain animal species The largest viruses (with dimensions of 225 to 400 mμ)—*e g* those of psittacosis and vaccinia—are but little smaller than certain bacteria and are in fact larger than pleuropneumonia organisms Between these two extremes the viruses form an almost unbroken series in regard to their size at one end the dimensions of viruses overlap those of protein molecules and at the other those of living microorganisms Vigorous discussion has centered around the question Are viruses living or nonliving entities? Viruses have certain properties which are usually attributed to living things as well as certain others which are usually associated with nonliving things and there is as yet no satisfactory basis upon which to determine the relative viability or nonviability of these infectious agents At the present time it is convenient to think of viruses as obligate intracellular parasites of very small size

The pathological changes resulting from infections by viruses depend primarily upon alterations in cell metabolism which are induced by the presence of a virus the nature of these aberrations is not fully understood It is known that different viruses affect the same cells in different ways and it is well established that certain viruses selectively infect different types of cells Consequently it would be expected that viral diseases might present exceedingly diverse clinical manifestations and that the ultimate pathological changes would be dissimilar This is in fact the case as will be evident from a consideration of the foregoing list of widely different infectious diseases each of which is either known or believed to be induced by a particular virus The primary pathological phenomena common to all viral diseases appear to be the following hyperplasia hyperplasia accompanied by necrosis and necrosis Some viral diseases are characterized by the occurrence of inclusion bodies in affected cells others do not show these peculiar morphological elements The exudative phenomena commonly associated with inflammation occur in varying degrees in most viral diseases but are thought to be secondary to the changes induced by the virus in cells of the infected tissues

An enduring immunity develops after many but not all viral diseases those not followed by persistent immunity are common cold influenza and herpes simplex This phenomenon serves additionally to distinguish viral infections from diseases caused by most other infectious agents The basis for the lasting immunity which follows most viral diseases is not known It is thought that changes induced as a result of the intimate association between virus and infected cell or the prolonged possibly persistent presence of some viruses in infected hosts may account for the continuing immunity It is because of the prolonged active immunity of many viral diseases that specific prophylactic measures have been so effective in protecting against some of them *e g* smallpox and yellow fever

At the present time almost no effective specific therapeutic measures have been devised for viral diseases However some diseases caused by the largest of known viruses—*e g* the psittacosis lymphogranuloma venereum group—appear to be favorably influenced by various chemotherapeutic substances Therapy with specific antiserum apparently is of no value once clinical manifestations of the infection have ensued since by this time the virus is widely disseminated in the infected tissues and most susceptible cells have already been affected During the incubation period that is before wide dissemination of the virus has occurred specific immune serum appears to be useful as a preventive measure in a few viral diseases *e g* measles

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Common Upper Respiratory Disease

(The Common Cold Adenoviral Infections)

The term "common upper respiratory disease is used to denote a group of infections of the upper respiratory tract presumably of viral origin which are world wide in distribution and to which the human race is almost universally susceptible Common respiratory disease is by all odds the most

fairly abrupt and the first symptom is likely to be a sensation of soreness and dryness localized to a small area of the pharynx Within a few hours a sense of congestion develops in the nasal passages usually accompanied by sneezing and shortly thereafter by nasal discharge which in the early stages is thin and watery At the end of forty-eight hours the full blown clinical picture has ordinarily developed the eyes are suffused the voice is husky there is fairly intense congestion of the upper respiratory mucosa with obstructed breathing nasal discharge is abundant the sense of smell and taste are diminished and there is some cough Unless the patient has a tendency to chronic bronchitis the cough is usually nonproductive in the early stages later on there may be some mucoid sputum Along with these local symptoms there is a variable amount of general malaise The patient feels lethargic and may complain of some vague aching pains in the back and limbs Marked malaise and prostration are not features of the common cold in adults however and the ordinary case is afebrile throughout

In children the disease is likely to be more severe and temperatures of 102 F or even higher are frequently noted Malaise is more pronounced and anorexia is common Other digestive symptoms are rare

Once the full symptoms have developed the common cold runs a variable course The whole illness may subside rapidly More commonly however there is a period of several days of excessive nasal secretion and cough with thick mucopurulent discharge which then gradually begins to abate Ordinarily the uncomplicated cold lasts from seven to fourteen days

Precisely where the common cold ends and complications begin is a matter of definition Some degree of laryngitis and tracheitis may be part of the primary picture but clinical signs of tracheobronchitis are properly to be considered as complications in all likelihood due to secondary bacterial infection Similarly it seems probable that there is some inflammation of the paranasal sinuses as part of the uncomplicated cold yet acute clinical sinusitis (which may occur late in the course of a cold) is a complication Otitis media is mainly a problem for the pediatrician It occurs most often in infancy and early childhood and may appear at any stage of the disease although most often it is fairly early It is more common in the winter months and is caused by the common respiratory bacterial pathogens

Diagnosis The characteristic appearance of a person with a full blown cold in the head is too familiar to require further comment Some mention however should be made of the appearance of the throat Close inspection will usually reveal a slightly shiny and edematous appearance of the mucous membrane with swelling and redness of the lymphatic aggregations Postnasal drip may be present but is not diagnostic True exudate on the tonsils or pharynx is not part of the picture of the common cold Such an exudate together with swelling and tenderness of the upper deep cervical lymph nodes indicates the presence of so-called "exudative pharyngitis" caused by infection with hemolytic streptococci or by an adenovirus On the whole however the adult pharynx particularly in heavy smokers may show little or no recognizable deviation from the normal in the course of an acute cold In children on the other hand the normal pharynx is usually paler and evidences of acute inflammation are thus much easier to detect

It must be borne in mind that there is a stage at the onset of certain specific diseases such as measles rubella chicken pox pertussis and cerebrospinal fever which may be indistinguishable from the common cold Moreover it is now known that infection with the viruses of influenza and atypical pneumonia may take the form of a mild disease simulating acute coryza These entities (in the absence of pneumonia) can only be differentiated from the common cold by serological means A purely allergic rhinitis may mimic the common cold In this situation the history is most important in differential diagnosis and the rapid development of symptoms the lacrimation sneezing itching and the pale boggy appearance of the turbinates are fairly characteristic An element of allergy may be present in infectious colds This is particularly true in some of the so-called "cold susceptible" children with a tendency to asthma In such instances the allergy is presumably directed toward bacterial products

There are no abnormal laboratory findings in the common cold If a leukocytosis is present it strongly suggests a bacterial complication

Finally it may be remarked that except in infancy the diagnosis of common cold is usually made by the patient not the physician His function is to exclude other conditions to search for complications and to institute appropriate therapy

Prophylaxis The prevention of any com

gether with certain remote rural populations (note Burkey's and Smillie's experience in Labrador and Alabama) appear to be much more susceptible to the activity of these bacteria than do adults in urban localities In all likelihood secondary infection with pathogenic bacteria in the young age and rural groups does intensify the local inflammation of the mucous membranes and heighten the constitutional reaction as well as prolongs the course Support for this view is derived from the fact that antimicrobial drugs do seem to modify the severity of colds in children in contrast to the adult experience cited before Thus it appears that most colds in adults unless they are accompanied by a purulent complication such as sinusitis or otitis are probably not much affected by the mere presence of a bacterial pathogen

In summary it can be stated that the common cold is due to one or more filterable viruses and that only in highly susceptible persons is there an etiological complex i e a bacterium acting in concert with a virus The bacterial effect may be either the general intensification of symptoms already referred to or a clear cut complication such as purulent sinusitis or otitis

It is to be noted that in the foregoing no reference has been made to chilling and exposure as factors in the etiology of colds This may be surprising since the very name of the malady presupposes an important etiological relationship Moreover it is mainly a disease of the colder months of the year and chilling of the body surface has been shown to cause vasoconstriction in the mucous membranes of the upper respiratory tract The latter observation lends some physiological basis to the notion that chilling may reduce local resistance to infection and thus supports the age old human belief that one can catch cold as a result of exposure It would be rash indeed to deny that chilling has any effect on the likelihood of catching cold It can be stated however that chilling in the absence of a primary infecting agent will not cause colds and that its role is at best a minor auxiliary one in an environment where primary agents are ubiquitous

Pathological Anatomy and Physiology In the presence of a cold there is an inflammation of the mucous membranes of the upper respiratory tract which often begins as a local affair in the throat The most intense reaction takes place in the nasal passages turbinates and so forth where a good deal of secretion mucoid at first and then mucopurulent is produced The principal pathological changes are edema hyperemia and hypersecretion with comparatively little cellular infiltration An appreciable amount of epithelial desquamation takes place as the disease progresses Stained smears of the secretions show considerable numbers of epithelial cells and leukocytes and the findings of eosinophils suggests that an allergic rhinitis is present

The effects of this disturbance are local and general With regard to the former in addition to the difficulty in breathing and the troublesome secretions there may be symptoms from blockage of the eustachian tubes or the paranasal sinuses The general effects presumably due to "absorption" are relatively minor particularly in adults

Epidemiology The epidemiology of colds can best be understood by remembering that they are highly communicable notably indoors and in childhood that the period of active immunity is short and that for reasons not entirely clear they appear mainly in the colder months of the year

Many surveys of the incidence of cold have yielded various estimates of their frequency depending on the age of the group under scrutiny its geographical location habitat and modus vivendi It seems likely that in urban communities in the temperate zone the general population averages about three colds a year This average number is often greatly exceeded in susceptible persons particularly children

When the weekly incidence of common respiratory diseases is charted for large masses of population there is ordinarily a low rate during the summer a rise in the autumn a single high midwinter peak and a spring decline When smaller urban groups are studied however a different pattern may appear in which not one but three peaks are discernible The first is in early autumn and all evidence would indicate that this is a result of the reopening of schools with the massing together of young susceptibles indoors The winter peak is often associated with an increased incidence of more severe respiratory infections such as pneumonia and may be accompanied by a wider dissemination of pathogenic bacteria Finally there may be a smaller secondary peak in the spring

As has been stated most colds appear to be communicable and transmitted directly by droplet infection Susceptibility being almost universal there is no practicable method of limiting the spread of colds under the ordinary conditions of urban life

Symptoms The onset of a cold is usually

Local therapy directed toward lessening secretions and improving the nasal airway is not recommended in the early acute stages of a cold Later on however when secretions have thickened it is often helpful not only in relieving symptoms but also in promoting sinus drainage One per cent ephedrine in saline used either in an atomizer or in the form of nose drops is safe and relatively nonirritating A propylhexedrine inhaler is convenient for the ambulatory patient

A few years ago the antihistaminic drugs were introduced as therapy for the common cold and it was claimed that if they were employed early enough the disease could be aborted in a large percentage of cases This received widespread publicity and in consequence of a tremendous advertising campaign these agents either by themselves or incorporated with other drugs have been taken by the public on a huge scale Subsequent carefully controlled studies have quite failed to substantiate the original claims The conclusions of the present writer based on an admittedly small series were that in perhaps one half of the cases the antihistaminics appeared to exert some benefit on the intensity of the catarrhal symptoms but that usually the fundamental course of the disease remained unchanged Fortunately these drugs in the dosages employed have been singularly innocuous as far as untoward side effects are concerned Nevertheless they are not recommended unless there is an allergic element present

The routine use of antimicrobial drugs in colds is contraindicated These drugs should be used only with a specific objective in mind *i e* the control of bacterial secondary infection In other words their use should be limited to those cases in which there is a strong likelihood that a complication is developing Thus clinical signs of bronchopulmonary infection sinusitis or otitis media are indications for their use The use of antimicrobial drugs may also be justified in highly susceptible persons who give a history of the regular occurrence of complications with their colds In such cases penicillin is the safest and most generally desirable agent A daily intramuscular injection of 1 ml of a mixture containing 300 000 units of procaine penicillin and 100 000 units of crystalline penicillin is recommended The suggestion of parenteral rather than oral penicillin is deliberate for the latter is so much easier to administer that it leads to much more indiscriminate use It must be borne in mind that as time goes on more and more persons disclose some sensitivity to penicillin and the drug should not be used without reasonable indications Obviously if it is employed the patient s past history in regard to penicillin therapy must be queried The tetracyclines and chloramphenicol are not recommended for routine use owing to their side effects

The treatment of subacute and chronic complications of the common cold is outside the scope of this discussion In adults the treatment of these complications usually falls into the purview of the otolaryngologist The pediatrician too is confronted with a small group of children often of the "allergic type who may be literally incapacitated by recurrent upper respiratory infections For such cases many expedients have been tried sulfadiazine or penicillin prophylaxis injections of stock and autogenous bacterial vaccines bacterial filtrates and similar procedures Change of climate is sometimes an essential recourse in the treatment of these recurrent respiratory infections Lastly it may be mentioned that in elderly people with chronic pulmonary emphysema and a tendency to bronchitis antimicrobial therapy is often indicated from the onset of an acute cold

ADENOVIRAL INFECTIONS

In 1953 Rowe and others reported the discovery of masked viral agents from surgically removed human adenoids which produced cytopathogenic effects in tissue culture Almost immediately thereafter Hilleman and co workers described similar viral agents recovered from military personnel with acute respiratory disease (ARD) and produced serological evidence that they were the cause of the infection One of Hilleman s strains designated at the time 'RI 67 was subsequently studied by Dingle He had luckily preserved acute and convalescent sera from cases of ARD observed during World War II and the rise in antibody clearly demonstrated that RI 67 had been the cause of this disease a decade earlier These discoveries were obviously of major importance and have led to an enormous amount of research It was soon recognized that Rowe s and Hilleman s agents belonged to the same general group for which the title adenovirus" has now been adopted New information is constantly being made available about adenoviruses but there are now enough basic data so that it is safe to outline certain generalizations concerning them

Adenoviruses multiply readily in tissue cultures composed of various cell lines both

municable disease may be attempted by interrupting the lines of communication or increasing the resistance of the person In a disease such as typhoid fever both methods are used with success It is obvious that the common cold falls into a different category As the malady is ubiquitous and nonincapacitating strict isolation is not a practicable measure Under conditions of urban life exposure is inevitable This must not be construed as an argument for total defeatism When one is dealing with highly susceptible groups such as nursery schools every endeavor should be made to exclude children in the acute stages of a cold Attempts to effect quarantine in the home and the wearing of masks may be laudable but are usually doomed to failure Recently the use of germicidal aerosols and ultraviolet light barriers have been extensively studied It is obvious that these measures have a limited application but it has been shown that ultraviolet light if properly applied seems to prevent cross infection in nurseries It is costly however and warranted only when special small populations are at risk

Attempts to increase individual resistance to an infection may be either specific or general In regard to the first it may be stated that there is no specific vaccine against the common cold and vaccination with virus containing material has up to the present been unsuccessful Indeed in a disease which leaves so short a period of active immunity in its wake this is not surprising Moreover in experimental transmission of the common cold it has been shown that there is little resistance to homologous reinoculation after a brief period of time In a somewhat different category are the so called cold vaccines composed of mixed bacterial antigens which are supposed to enhance resistance to the secondary invaders On the whole these have been disappointing and most large controlled studies indicate that they are not effective in reducing the incidence of or invalidism from colds In the occasional patient who is highly susceptible to bacterial complications the vaccines have at times appeared to be of some limited benefit

The general measures are mainly concerned with nutrition hygiene 'hardening procedures and the eradication of focal diseased areas Here again the record is a disappointing one There is no statistical evidence in controlled studies that the state of nutrition the addition of vitamins in excess the type of clothing worn exposure to sunlight fresh air and similar measures have any effect on susceptibility to colds In regard to the presence of diseased tonsillar and adenoidal tissue there is some difference of opinion Though the removal of tonsils is generally admitted to influence recurrent severe streptococcal throat infections its effect on colds is debatable In all likelihood the presence of adenoid tissue influences the severity of colds in early childhood On the other hand surveys of older children indicate that there is little difference in cold susceptibility between those who have undergone tonsillectomy and adenoidectomy and those who have not

Long term chemoprophylaxis with small doses of sulfadiazine or oral penicillin will strikingly reduce the incidence of streptococcal infections There is also evidence that it may reduce the severity of common respiratory disease in highly susceptible infants or children In adults on the other hand such chemoprophylaxis appears to have relatively little effect

Treatment Up to the present no specific agent has been developed which is effective against the virus of the common cold In consequence therapy is directed at general management relief of symptoms and the control of complications

In ideal circumstances it would probably be advisable to treat all sufferers from the common cold with rest and isolation but in practice this is impossible Bed rest should however be enforced in the more highly susceptible *i e* infants and young children and in adults with temperatures over 100° F or some complicating chronic disease

Symptomatic relief in the very young can usually be afforded by small doses of acetyl salicylic acid (aspirin) In adults particularly if cough is troublesome it is customary to give some codeine as well This may be administered in the form of codeine cough mixture or in the traditional grippe capsule The following prescription has the weight of tradition behind it and is effective

Codeine sulfate	0 015 gm
Acetylsalicylic acid	0 3 gm
Phenacetin	0 12 gm
Caffeine citrate	0 03 gm

One of these capsules may be given every *three or four hours*

Capsules containing 0 015 gm each of codeine and papaverine are also popular and it has been suggested that they may aid in "aborting a cold In the writer s experience they do not do so but are merely symptomatic in their effect

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Influenza

(Grip Catarrhal Fever Epidemic Influenza)

Definition Influenza is a specific infectious disease of man caused by a virus of the influenza group The disease is an acute self limited infection and is characterized by constitutional symptoms although the infection is restricted to the respiratory tract It occurs most commonly in epidemics of varied size Between epidemics sporadic cases are encountered Three distinct etiological types of the disease are known *influenza A influenza B* and *influenza C* Influenza A occurs more commonly than influenza B influenza C appears to be rare A distinction between the etiological types cannot be made on clinical or pathological grounds The disease is usually of short duration and is rarely serious Complications are uncommon but may be severe particularly if secondary bacterial pneumonia develops The cause of the great pandemic of 1918–1919 has not been decisively established

History The disease has been recognized since ancient times Many widespread epidemics and occasional great pandemics have occurred during the past four centuries In recent times extensive pandemics appeared in 1889–1892 and 1918–1919 The latter affected persons in all areas of the earth and is thought to have led to the death of about 20 000 000 people Much the most common cause of death was secondary bacterial pneumonia

Modern knowledge of influenza stems from the discovery by *Smith Andrewes and Laidlaw in 1933* that the disease is caused by a virus This agent is now designated influenza A virus Epidemics of varying extent have occurred frequently during the past twenty years recently they have appeared almost yearly but the disease involved has not been commonly associated with complications In 1940 Francis and Magill independently discovered influenza B virus This agent is unrelated antigenically to influenza A virus one does not produce immunity against the other That the two major types of influenza now designated A and B are caused by influenza A virus and influenza B virus respectively is generally accepted In 1949 Taylor discovered influenza C virus This agent is unrelated antigenically to either influenza A or B virus Relatively few patients with influenza C have been studied and far less is known of this disease than of influenza A or B In the absence of satisfactory material from patients with the pandemic disease of 1918–1919 it has not been possible to determine whether any of the known influenza viruses or some other infectious agent was the primary causal factor

Etiology The disease is caused by a virus of the influenza group This agent is spherically shaped and of medium size about 100 $m\mu$ in diameter During the acute phase of the disease the virus is present in the respiratory tract but not in other areas of the body nor in the blood Sputum saliva and nasal secretions contain the agent It can be demonstrated in washings of the nose or throat from the first day of illness to the fifth There are three distinct and immunologically unrelated serological types *influenza A influenza B* and *influenza C* virus Influenza A and B viruses are infective for ferrets mice hamsters and chick embryos Influenza C virus appears to be infective but less virulent for most of these species although it has not caused infection in mice Animals appear not to be infected by these agents in nature and there is no evidence for an interepidemic reservoir for the viruses other than man himself Usually the agents are recovered from throat washings of patients by inoculation into the amniotic sac of chick embryos With the exception of swine influenza virus which is immunologically related to some strains of influenza A virus no other virus is known to be serologically related to any of the agents in the influenza group Progressive variation in antigenic composition particularly marked with influenza A and B viruses is more striking than with any other virus infecting man and has seriously affected efforts to prevent the disease with

vaccines Influenza viruses like vintage wines vary unpredictably from year to year Influenza A virus has shown particularly striking alterations In 1946–1947 the antigenic composition changed so much that vaccines made from earlier strains became ineffective the new strains were designated A prime " In 1957 even more marked alterations in antigenic composition occurred which again made earlier vaccines obsolete and resulted in the much publicized designation Asian" influenza

Infection or immunization with influenza A virus does not lead to immunity against influenza B or C virus and vice versa Despite these striking immunological differences the agents possess many common properties One of the most useful is their capacity to cause agglutination of erythrocytes *in vitro* a reaction which has provided simple techniques for identification and measurement of the viruses or antibodies against them An increase in antibodies against the type of virus which caused the infection may be demonstrated seven to ten days after the onset of illness the maximal antibody response is observed two to four weeks after onset Antibody levels against a soluble antigen of the virus are measured by complement fixation against the virus itself by hemagglutination inhibition or by neutralization *in vivo* Because may persons of school age or older possess antibodies against each of the three types of virus in their serum measurement of the antibody levels in a single serum specimen is not helpful in reaching an etiological diagnosis A comparison of the antibody levels in acute phase and convalescent serum specimens is the most reliable means of establishing the diagnosis and the etiological type of the disease

Incidence and Epidemiology Although occasional sporadic cases occur during interepidemic periods they do not often lead to many secondary cases among contacts Influenza appears most commonly in epidemics which may be localized or widely spread During the past twenty years epidemics have broken out in some parts of the world almost annually Localized epidemics may appear nearly at the same time in different areas even in different countries or large epidemics may seem to spread from one area or country to another Pandemic outbreaks have appeared only rarely and have been separated by long intervals of varying duration The pandemics of 1889–1892 and 1918–1919 which were of undetermined etiology were separated by about twenty nine years those of 1918–1919 and 1957 *i e* "Asian" influenza by about thirty nine years

Although epidemics tend to appear during winter months they may occur at any time of the year even in the summer Large epidemics show some cyclic tendency those of influenza A have occurred at about two to three year intervals while those of influenza B have appeared roughly at four to five year intervals Epidemics of influenza A tend to be more extensive than those of influenza B Occasionally the two diseases occur in the same epidemic and rarely concurrent infection with the two viruses may develop in the same patient The attack rate may vary widely in different epidemics from as low as 1 to 2 per cent to as high as 20 to 30 per cent Usually the more crowded the conditions of living the higher is the attack rate Under conditions of crowding epidemics build up rapidly and then quickly "burn out " the whole occupying no more than two to three weeks In dispersed populations events are less dramatic and the epidemic may smolder along for two to three months

Persons of any age or race and of either sex are about equally susceptible Transmission is probably through infective droplets distributed from the upper respiratory tract which is also the portal of entry for the virus The existence of persistent carriers of influenza virus has not been demonstrated It is thought that the viruses are maintained during interepidemic periods by a chain of sporadic infections in man Infection with the agents is very common and after five years of age most persons possess specific antibodies in their serum Inapparent or subclinical infections are at least as frequent as is the manifest disease and account in part for the high incidence of antibodies against the viruses in the serum of healthy persons Neither influenza A nor B leads to persistent immunity second infections of the same type may develop after six to eight months Influenza A induces no immunity to influenza B and *vice versa* Resistance to infection is directly correlated with the type specific antibody level in the serum the higher the titer the less likely is infection

Morbid Anatomy Little is known of the pathological alterations associated with uncomplicated influenza in man In the ferret the virus causes necrosis of the respiratory epithelium of the nasal mucous membrane In man fatal attacks are commonly complicated by secondary bacterial infection

Many of the pathological changes seen may be largely attributable to the latter In such cases there is tracheal and bronchial inflammation with marked epithelial desquamation and some epithelial necrosis Extensive bronchopneumonia or interstitial pneumonia is usually present During the 1957 outbreak some fatal cases occurred without evidence of bacterial infection In most instances there were antecedent cardiac valvular lesions and extensive hemorrhage and inflammation was found in the lungs

Pathological Physiology and Chemistry The leukocyte count is commonly within the normal range Leukopenia when it occurs is found early in the disease usually in patients with high fever and marked symptoms The differential leukocyte pattern is usually normal even if leukopenia is present The erythrocyte sedimentation rate is increased The urine is usually normal although slight albuminuria may occur In the uncomplicated disease cyanosis is not present cultures of the blood are sterile and the roentgenogram does not show evidence of pneumonia in the great majority of patients The evidences of toxicity and the marked prostration so commonly seen may be attributable to toxic properties of the virus itself

Symptoms Both influenza A and B lead to an array of clinical pictures which vary widely in severity and duration Neither of the infections produces signs or symptoms which are pathognomonic Too little is known as yet about influenza C to permit generalization

The incubation period of influenza A or B is usually only one or two days and the onset generally is abrupt The first and most prominent symptoms are constitutional In the more typical cases these are commonly chilliness or a frank chill fever headache malaise lassitude anorexia and muscular pains Prostration of varying degree is common Symptoms referable to the respiratory tract usually are not marked and consist of sneezing nasal irritation or discharge fullness or irritation of the nasopharynx larynx or trachea Cough is common but usually is not productive Epistaxis hoarseness nausea or substernal pain may develop In the less typical cases similar symptoms usually appear but may vary markedly in degree In some patients the disease may simulate any of the minor acute respiratory infections In other patients the disease may resemble more severe or generalized infections

Fever is commonly remittent and usually persists for two or three days the range is one to six days Generally the highest temperature is between 101° and 103° F though in the more severe cases it may reach 105° F Commonly the fever is highest on the first or second day of disease The pulse rate is increased generally in proportion to the fever and may be quite rapid The respiratory rate is normal or only slightly increased

Physical signs usually are neither definite nor striking The face may be flushed and the conjunctivae are sometimes injected The nasal mucosa may be somewhat injected and swollen The fauces soft palate and posterior pharynx may be mildly injected and the lymphoid follicles may be prominent The physical signs over the chest are usually normal although fine moist rales may be found in the lower lung fields posteriorly Definite signs of pulmonary consolidation occur only in rare instances and commonly are indicative of secondary bacterial infection The remainder of the physical examination does not ordinarily reveal abnormal findings attributable to influenza

Course and Complications The severity of the infection and the course of the illness vary widely Usually patients are not acutely ill for more than three to five days though some may be miserable for a week or more The fever tends to come down by lysis and thereafter symptoms gradually disappear Convalescence is commonly uneventful and may be fairly rapid in previously healthy persons Patients with marked symptoms may complain of considerable prostration increased sweating and fatigability for a week or more after fever has disappeared

The infections which occurred during the pandemic disease of 1918–1919 were in general more severe than those which have developed during the two decades since influenza viruses were discovered In this pandemic pneumonia appeared in many patients and was the major cause of death Usually the first evidence of pneumonia developed two to four days after the onset In some patients very severe or fulminating infections occurred and rapidly were fatal In others pneumonia did not develop until the acute phase of the initial infection was over The pneumonia was attributable to bacterial infection in almost every instance and a variety of bacterial species was associated with the infection Staphylococci beta hemolytic streptococci *H influenzae* and pneumococci were the most frequent invaders Infection of the pleura and empyema were common complications usually

associated with beta hemolytic streptococci or pneumococci Occasionally lung abscess developed following staphylococcal or beta hemolytic streptococcal infection Bronchiectasis chronic bronchitis or pulmonary fibrosis sometimes developed

In striking contrast is the experience of the past two decades with epidemics of influenza of known cause During this period previously healthy persons who contracted either influenza A or B only rarely developed serious complications A small number of attacks of influenza have been associated with staphylococcal pneumonia and some with pneumococcal pneumonia but in the great majority of patients frank pulmonary disease has not occurred

The experience gained during the extensive outbreak of 1957 has raised the possibility that in patients with marked cardiac disease pulmonary infection with the virus can be serious and perhaps fatal

Diagnosis During an epidemic of influenza the diagnosis is usually not difficult because of the fairly typical clinical picture presented by the majority of patients Common features are abrupt onset with fever headache prostration muscular pains cough and nasal symptoms in the absence of markedly abnormal physical signs During interepidemic periods sporadic cases though presenting somewhat similar clinical pictures are difficult to diagnose without aid from the laboratory

A number of other infectious diseases may closely resemble influenza Among these are undifferentiated acute upper respiratory infections primary atypical pneumonia paranasal sinusitis abortive measles dengue Rift Valley fever lymphocytic choriomeningitis and Venezuelan equine encephalomyelitis In some instances influenza can be distinguished from these diseases only by laboratory procedures

Infection with either influenza A or B virus may cause a wide variety of clinical pictures ranging from very mild to moderately severe illnesses During epidemics subclinical or inapparent infections not associated with definite symptoms are common Influenza A may lead to somewhat more marked symptoms than influenza B but the clinical findings do not distinguish one from the other

An etiological diagnosis can be established only by laboratory procedures The virus may be recovered from the upper respiratory tract during the acute phase of the illness The virus cannot be recovered from the blood cerebrospinal fluid or feces A specific antibody response to the infecting virus may be demonstrated with appropriate serum specimens by various immunological techniques Complement fixation virus neutralization and hemagglutination inhibition procedures can all yield satisfactory results Two specimens of serum are needed from each patient one should be obtained less than five days after onset the other two or three weeks later Before throat washings or serum specimens are obtained the laboratory which is to carry out the tests should be consulted

Prognosis In previously healthy children or adults the prognosis is excellent and an uneventful recovery may be anticipated in the great majority of patients In undernourished or debilitated persons those with chronic diseases or persons of advanced age the prognosis may not be as good Such patients appear to be more liable to develop secondary bacterial infections of the respiratory tract and pneumonia may arise Under these circumstances the prognosis becomes that usually associated with the particular bacterial infection Antimicrobial therapy appears to be about as effective in controlling secondary bacterial infection associated with influenza as in similar infections in the absence of the viral disease

In the rare instances in which the virus invades the lungs antimicrobial therapy is of no avail

Prognosis In previously healthy children vaccines capable of inducing temporarily increased resistance to influenza A and B have been developed and gradually improved The currently available vaccines contain a number of strains of both viruses which have been inactivated and to some degree purified from the allantoic fluid of *infected chick embryos Subcutaneous or* intramuscular injection of such a vaccine usually results in the production of antibodies against the viruses in the vaccine An increase in the antibody levels of the serum begins about a week after injection of the vaccine and the maximal antibody response is present at about two weeks After another month or six weeks the increased antibody levels gradually decline To a considerable extent the degree of increase in resistance to infection with either influenza A or B virus is directly correlated with the serum antibody level

Vaccination leads in general to reduced susceptibility to infection for some months estimates range from two to twelve months Protection is not complete and vaccinated persons can still contract the disease Avail

able vaccines although capable of diminishing the likelihood of infection are effective for a relatively short period As a consequence they are most useful when given shortly before an epidemic Predictions on the occurrence of epidemics are notably unreliable Influenza virus vaccines possess toxic properties and if a sufficient quantity is injected may lead to unpleasant symptoms especially in children In addition they contain some chick embryo material which is antigenic This may induce sensitization or in rare instances lead to serious reactions in persons hypersensitive to egg products

Treatment Effective chemotherapy against the viral infection has not yet been developed Supportive and symptomatic treatment similar to that used in other acute upper respiratory infections provides some relief During the febrile period the patient should remain in bed large quantities of fluid should be taken and the diet should be liquid or light Acetylsalicylic acid 0 3 to 1 0 gm and codeine 0 016 to 0 032 gm are the drugs most commonly employed Barbiturates may be used to control sleeplessness Sulfonamide drugs and penicillin even in large doses are ineffective Similarly the tetracyclines and chloramphenicol do not favorably affect the course of the disease The injection of influenza virus vaccine after the disease has appeared is not beneficial and may increase symptoms

Because secondary bacterial infections occur in only a small proportion of patients it is in general unwise to attempt to prevent their development with antimicrobial drugs However when definite bacterial infection does develop appropriate chemotherapy should be instituted and carried out as it would be in the absence of the viral infection This is especially important when bacterial pneumonia appears

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Dengue

Definition Dengue is an acute febrile nonfatal disease of viral etiology characterized by localized and generalized aches and pains prostration exanthema lymphadenopathy and leukopenia *Transmission is by* bite of mosquitoes specifically of genus Aedes Two antigenically distinct types of dengue virus are known which belong to the family of group B arthropod borne (Arbor) viruses

Etiology Dengue virus can be isolated from patients blood during the febrile phase of the disease Serum obtained on the first day of fever contains about 1 000 000 infectious doses per ml The virus can be inactivated by heating at 56 C for thirty minutes by ultraviolet light or by treatment with 0 05 per cent formalin Inactivation by these methods also destroys the immunogenic capacity of the virus Infectivity can be preserved for many years by freezing or lyophilizing The viral elementary body assuming that it is spherical has a diameter of 17 to 25 $m\mu$

During World War II Sabin and Schlesinger in the United States and Hotta in Japan succeeded in adapting dengue virus to mice This opened the way to intensive studies on the properties of dengue virus and its relationship to other agents When first isolated from the blood of sick patients the virus is usually not pathogenic for laboratory animals In the course of serial intracerebral passages in baby mice the virus undergoes progressive modifications This manifests itself in the form of gradually emerging virulence—first for suckling mice only later also for adult mice—and the ability to multiply in chick embryos and in monkey kidney tissue cultures The modified virus causes fatal encephalomyelitis in mice Adaptation of the virus to the mouse or chick embryo is associated with attenuation of its pathogenicity for man Human beings inoculated with modified virus experience none of the debilitating signs and symptoms of dengue but they develop a typical rash and subsequently are immune to infection with unmodified virus of the same serological type

The existence of two serological types (I and II) was first discovered in cross immunity tests in human volunteers later verified by neutralization tests in mice Complement fixing and hemagglutinating antigens can be extracted from infected tissues Serological tests with such antigens have revealed cross reactions not only between the two types of dengue virus but also between these and other members of the group B arthropod borne ("Arbor") viruses (such as yellow fever Japanese B St Louis encephalitis West Nile and others)

Incidence and Epidemiology Dengue has been known as an epidemic disease since the late eighteenth century Since 1920 very extensive epidemics have occurred in the United States (Gulf Coast) Greece Australia and Japan In such epidemics the disease may affect 40 to 80 per cent of the

population of cities Epidemics of such proportions are undoubtedly due to the im portation of the virus into a nonimmune population at a time when suitable insect vectors abound In other areas notably the Southwest Pacific islands Queensland and New Guinea Indonesia the Philippines portions of India Malaya Burma and Indo china and perhaps sections of Africa the disease is endemic Newcomers to endemic areas incur a high risk of acquiring the disease

Infection is transmitted from man to man by the bite of mosquitoes of the genus Aedes Species definitely incriminated as vectors are *Aedes aegypti* *Aedes albopictus* *Aedes scutellaris* and *Aedes polynesiensis* Marks After engorgement with infectious blood an extrinsic incubation period of eight to fourteen days is required before *A aegypti* can transmit the virus The bite of a single infected mosquito is enough to produce the disease and the insects once infected remain capable of transmitting the virus for the rest of their lives Inapparent infection with dengue virus can be pro duced in monkeys and these animals may play a role as intermediate or alternate hosts Recent findings by Smith in Malaya suggest on the basis of serological evi dence that monkeys and certain other tree living animals may be intermediate hosts to the virus and that *A albopictus* may be responsible for transmission among these species as well as for endemic persistence of virus in rural areas Spread from these areas to urban centers leading to localized outbreaks seems to be precipitated by inva sion by *A aegypti* The latter being domes tic in its habits is probably responsible for large scale epidemics The possibility that Haemagogus mosquitoes may play a role in the transmission of "jungle dengue" has also been suggested

Morbid Anatomy Dengue is a nonfatal disease it is dubious whether the reported postmortem findings in alleged uncompli cated cases were typical of dengue Sabin found that tissue obtained by biopsy of cutaneous eruptions showed marked vascu litis with endothelial swelling and peri vascular edema and infiltration with mono nuclear cells

Symptoms The incubation period aver ages five to eight days The onset is usually sudden with a sharp rise in temperature associated with chills excruciating head ache retro-ocular pain—especially on move ment of the eyeballs—photophobia back ache pain in muscles and joints At this time there is no distinct rash but the face is flushed and the skin may be diffusely mottled Fever persists for five to six days at 103 to 105 F Occasionally the tem perature returns to normal or nearly normal about the third day then rises again thus giving the classic (but rare) saddle back fever curve In addition to the symptoms already listed others referable to various organ systems are frequently encountered *e g* altered taste sensations sore throat marked anorexia and constipation colicky pain abdominal tenderness hyperesthesia of the skin and drawing pain in the ingui nal region and testicles The most constant and characteristic symptoms however are headache pain on movement of the eye balls photophobia and the severe general ized aches and pains which have earned the disease the name "breakbone fever" The marked discomfort combined with a tend ency to be depressed and extremely weak causes the patient to take a very dim view of his chances of recovery

Although absence of rashes has been ob served in various proportions of patients in spontaneous dengue epidemics the experi mentally produced disease is almost in variably associated with an intense maculo-papular eruption spreading over the entire body This appears usually about the third or fourth day of fever The rash fades on pressure Later at defervescence nonfading petechial hemorrhages may be superim posed at certain sites *e g* on the insteps in skin folds in areas exposed to pressure from clothing or bandages and on the oral mucosa Lymph nodes are often enlarged but are not tender

The disease is associated with marked leukopenia As a rule the total leukocyte count decreases at the onset of fever and remains at 2000 to 3000 per cu mm during the acute phase Initially there are lymphopenia and a marked increase in immature neutrophile leukocytes Toward the end of the febrile phase there may be a change in the direction of relative lympho-cytosis

In epidemics patients are often seen with relatively mild disease shorter in duration than the typical syndrome and not associ ated with rash On the basis of experimental findings it has been suggested that such mild episodes may be due to second infec tions of persons partially immune as a result of previous infection with an im munologically distinct strain of virus

Immunity The existence of immunity to reinfection was inferred years ago from epidemiological evidence *e g* from the dif ferences in incidence of dengue among

able vaccines although capable of diminishing the likelihood of infection are effective for a relatively short period As a consequence they are most useful when given shortly before an epidemic Predictions on the occurrence of epidemics are notably unreliable Influenza virus vaccines possess toxic properties and if a sufficient quantity is injected may lead to unpleasant symptoms especially in children In addition they contain some chick embryo material which is antigenic This may induce sensitization or in rare instances lead to serious reactions in persons hypersensitive to egg products

Treatment Effective chemotherapy against the viral infection has not yet been developed Supportive and symptomatic treatment similar to that used in other acute upper respiratory infections provides some relief During the febrile period the patient should remain in bed large quantities of fluid should be taken and the diet should be liquid or light Acetylsalicylic acid 0 3 to 1 0 gm and codeine 0 016 to 0 032 gm are the drugs most commonly employed Barbiturates may be used to control sleeplessness Sulfonamide drugs and penicillin even in large doses are ineffective Similarly the tetracyclines and chloramphenicol do not favorably affect the course of the disease The injection of influenza virus vaccine after the disease has appeared is not beneficial and may increase symptoms

Because secondary bacterial infections occur in only a small proportion of patients it is in general unwise to attempt to prevent their development with antimicrobial drugs However when definite bacterial infection does develop appropriate chemotherapy should be instituted and carried out as it would be in the absence of the viral infection This is especially important when bacterial pneumonia appears

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Definition Dengue is an acute febrile nonfatal disease of viral etiology characterized by localized and generalized aches and pains prostration exanthema lymphadenopathy and leukopenia Transmission is by bite of mosquitoes specifically of genus Aedes Two antigenically distinct types of dengue virus are known which belong to the family of group B arthropod borne ("Arbor") viruses

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During World War II Sabin and Schlesinger in the United States and Hotta in Japan succeeded in adapting dengue virus to mice This opened the wa to intensive studies on the properties of dengue virus and its relationship to other agents When first isolated from the blood of sick patients the virus is usually not pathogenic for laboratory animals In the course of serial intracerebral passages in baby mice the virus undergoes progressive modifications This manifests itself in the form of gradually emerging virulence—first for suckling mice only later also for adult mice—and the ability to multiply in chick embryos and in monkey kidney tissue cultures The modified virus causes fatal encephalomyelitis in mice Adaptation of the virus to the mouse or chick embryo is associated with attenuation of its pathogenicity for man Human beings inoculated with modified virus experience none of the debilitating signs and symptoms of dengue but they develop a typical rash and subsequently are immune to infection with unmodified virus of the same serological type

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Incidence and Epidemiology Dengue has been known as an epidemic disease since the late eighteenth century Since 1920 very extensive epidemics have occurred in the United States (Gulf Coast) Greece Australia and Japan In such epidemics the disease may affect 40 to 80 per cent of the

several times a day particularly the short hair of the neck and all ticks removed The feeding or attached tick is removed with some difficulty the best method being to apply some irritant such as turpentine iodine or acetone Then the tick can be teased out of the skin by inserting a needle between the mouth parts Should the mouth parts be left in the skin a small shallow indolent ulcer is likely to develop

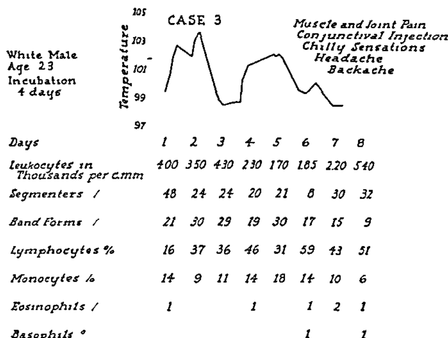
The virus is transmitted transovarially and consequently the infection is self perpetuating in the tick No animal host has as yet been demonstrated It is easy to infect the hamster or newborn mice with blood from a patient

No one has ever been reported to have had the disease twice

Morbid Anatomy Pathological Physiology Only one death has been reported consequently little is known about pathological changes in the tissues Like dengue however the disease causes a definite reduction in the leukocyte count Counts lower than 2000 per cu mm are frequently recorded the low point usually occurring during the second attack All of the leukocytes are reduced in absolute numbers except the monocytes There is a marked increase in the band forms Hematological recovery follows clinical recovery by four to seven days

Symptoms and Clinical Course The onset is sudden with chilly sensations and mild photophobia This is quickly followed by generalized aching especially in the muscle and tendon insertions around the joints The other prominent features of this aching consist of headache deep ocular pain and backache particularly in the lumbar region Anorexia and nausea are common Vomiting occurs in children The first attack lasts approximately two days followed by a complete remission of all signs and symptoms for about the same length of time The second attack usually lasts somewhat longer than the first Either episode may be more severe than the other Although the usual pattern is for an attack and the remission to last approximately two days each variations of one to four days do occur Third attacks have been reported A single episode lasting five to seven days is likewise possible While disappearance of symptoms occurs rapidly at the end of the second attack the patient usually has a period of four to five days of mild lassitude Figure 1 is typical of most of the cases recognized in the western states

Diagnosis The diagnosis is made on the basis of the following criteria (1) A history of having been bitten by a tick or having been in a tick infested area four to six days prior to onset (2) A fever curve and symptoms identical with dengue The temperature rises rapidly to 102° to 104° F and occasionally to 105 F During the remission it is frequently subnormal (3) Absence of physical findings other than fever with a corresponding increase in pulse rate



Days	1	2	3	4	5	6	7	8
Leukocytes in Thousands per c.mm	400	350	430	230	170	185	220	540
Segmenters /	48	24	24	20	21	8	30	32
Band Forms /	21	30	29	19	30	17	15	9
Lymphocytes %	16	37	36	46	31	59	43	51
Monocytes /o	14	9	11	14	18	14	10	6
Eosinophils /	1			1		1	2	1
Basophils °						1		1

FIG 1 Colorado tick fever

native soldiers and recently arrived American troops stationed together in the Philippine Islands Experimentally infected volunteers retain solid immunity to reinfection with homotypic virus for years but early reinfection with a heterologous strain may lead to mild second disease (see above) In line with this type specific neutralizing antibodies persist in the serum for many years while cross neutralization of heterologous strains is absent or weak

Diagnosis The disease is easily diagnosed on clinical grounds when it is fully developed Dengue should always be suspected when febrile illnesses of the type described occur in suitable epidemiological environments Specific differentiation from other febrile illnesses with similar symptoms rests on serological confirmation The neutralization test is type specific in primary infection while complement fixation and hemagglutination inhibition reactions cross with other group B Arbor antigens The specificity of any serological response may be doubted however in inhabitants of an area in which more than one group B Arbor virus are endemic or in persons previously vaccinated against yellow fever Under these conditions previous sensitization may lead to a broad group specific anamnestic antibody response which extends even to neutralizing antibody

Prognosis Uncomplicated dengue is not fatal but complete recovery may take several weeks Convalescence is characterized by prolonged weakness and sometimes by mental depression

Treatment and Prevention Treatment of the acute disease is entirely nonspecific and should include absolute bed rest maintenance of fluid and electrolyte balance and alleviation of discomfort Acetylsalicylic acid 0 3 to 0 6 gm alone or in suitable combination with phenacetin and caffeine should be given every three to four hours (Salicylates may produce marked aberrations from the typical fever chart) Severe pains may necessitate oral or subcutaneous administration of codeine sulfate 30 to 60 mg Other therapeutic measures should be designed to keep the patient as comfortable as possible Complications should be anticipated recognized and treated as indicated Resumption of normal activities should not be rushed a two week period of convalescence is desirable and often needed

The most practicable method of prevention is eradication of mosquito vectors Vaccines prepared from infected mouse brain or chick embryo have been effective in experiments on human volunteers and their use may be considered under conditions of critical need

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Colorado Tick Fever

Definition and Etiology Colorado tick fever is a distinct disease entity of viral etiology transmitted by ticks It is clinically indistinguishable from dengue except for the absence of a rash

Incidence, Epidemiology and Prevention The disease is unfortunately named since it has been reported in all the western states in which the wood tick *Dermacentor andersoni* is found In Colorado it is by far the most common of the tick borne diseases probably outnumbering Rocky Mountain spotted fever 100 to 1 Although it has never been reported on the eastern seaboard the virus has been isolated from Long Island dog ticks *Dermacentor variabilis* Colorado tick fever therefore is probably not confined to the west but like Rocky Mountain spotted fever will be found in other parts of the United States

The disease occurs in the spring and early summer when the ticks are active Invariably the victim has been in a tick infested area four to six days prior to onset In most cases either the patient will have found the feeding tick prior to the illness or a careful search at the time of onset will demonstrate it The person involved is not aware of the presence of this arthropod since the bite is painless Persons who visit in the mountains particularly if they walk through tall grass and low shrubs are likely to pick up one or more ticks The entire body should be thoroughly inspected

several times a day particularly the short hair of the neck and all ticks removed The feeding or attached tick is removed with some difficulty the best method being to apply some irritant such as turpentine iodine or acetone Then the tick can be teased out of the skin by inserting a needle between the mouth parts Should the mouth parts be left in the skin a small shallow indolent ulcer is likely to develop

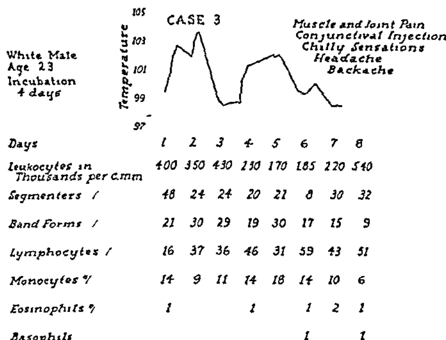
The virus is transmitted transovarially and consequently the infection is self perpetuating in the tick No animal host has as yet been demonstrated It is easy to infect the hamster or newborn mice with blood from a patient

No one has ever been reported to have had the disease twice

Morbid Anatomy, Pathological Physiology Only one death has been reported consequently little is known about pathological changes in the tissues Like dengue however the disease causes a definite reduction in the leukocyte count Counts lower than 2000 per cu mm are frequently recorded the low point usually occurring during the second attack All of the leukocytes are reduced in absolute numbers except the monocytes There is a marked increase in the band forms Hematological recovery follows clinical recovery by four to seven days

Symptoms and Clinical Course The onset is sudden with chilly sensations and mild photophobia This is quickly followed by generalized aching especially in the muscle and tendon insertions around the joints The other prominent features of this aching consist of headache deep ocular pain and backache particularly in the lumbar region Anorexia and nausea are common Vomiting occurs in children The first attack lasts approximately two days followed by a complete remission of all signs and symptoms for about the same length of time The second attack usually lasts somewhat longer than the first Either episode may be more severe than the other Although the usual pattern is for an attack and the remission to last approximately two days each variations of one to four days do occur Third attacks have been reported A single episode lasting five to seven days is likewise possible While disappearance of symptoms occurs rapidly at the end of the second attack the patient usually has a period of four to five days of mild lassitude Figure 1 is typical of most of the cases recognized in the western states

Diagnosis The diagnosis is made on the basis of the following criteria (1) A history of having been bitten by a tick or having been in a tick infested area four to six days prior to onset (2) A fever curve and symptoms identical with dengue The temperature rises rapidly to 102 to 104 F and occasionally to 105 F During the remission it is frequently subnormal (3) Absence of physical findings other than fever with a corresponding increase in pulse rate



Days	1	2	3	4	5	6	7	8
Leukocytes in Thousands per c.mm	400	350	430	230	170	185	220	540
Segmenters %	48	24	24	20	21	8	30	32
Band Forms %	21	30	29	19	30	17	15	9
Lymphocytes %	16	37	36	46	31	59	43	51
Monocytes %	14	9	11	14	18	14	10	6
Eosinophils %	1			1		1	2	1
Basophils						1		1

FIG 1 Colorado tick fever

slight erythema of the skin and conjunctival injection (4) A reduced leukocyte count with an increase in immature forms (5) Other confirmatory laboratory tests usually unnecessary in the typical case

Complement fixation tests during the acute phase and three weeks following recovery may be a useful procedure The first test should be negative and the second positive Injection intraperitoneally or intracerebrally into baby mice or baby hamsters of blood serum obtained during any phase of the disease will cause the death of these animals while neutralization of the virus with immune serum results in survival

Care must be exercised not to confuse Colorado tick fever with the much more severe and frequently fatal Rocky Mountain spotted fever especially since specific treatment is available for the latter The difference in severity between the two is most helpful while the rash of Pocky Mountain spotted fever will always differentiate the two There is no disease in the United States with which typical Colorado tick fever should be confused except dengue The mode of spread and the frequent presence of a rash in dengue suffice to differentiate them Colorado tick fever is not a tick borne dengue since neither disease gives an immunity to the other although each confers immunity to itself

Prognosis The prognosis is excellent Complications or sequelae have been infrequently observed The virus is always found in the cerebrospinal fluid No increase in pressure or other abnormalities of the fluid have been observed except in the occasional patient who develops encephalitis

Treatment Treatment is symptomatic Acetylsalicylic acid in standard doses is usually sufficient to reduce the fever and aching There is no evidence that any of the available antimicrobial drugs is of value

LLOYD FLORIO

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Yellow Fever

Definition Yellow fever is an acute viral disease characterized by sudden onset prostration moderately high fever a pulse rate slow in relation to temperature and when severe by vomiting of altered blood albuminuria and jaundice It is endemic in the tropical rain forests of Africa and South America in the past summer epidemics have been widespread in the temperate zone There are two epidemiological types of the disease When the virus is transmitted from man to man by the domestic mosquito *Aedes aegypti* it is called *urban yellow fever* but when it occurs in a forest environment and is transmitted to man by some forest mosquito usually in the absence of *A aegypti* it is called *sylvan (or jungle) yellow fever*

Etiology and Epidemiology Yellow fever virus is a group B arborvirus according to Casals new serological classification of viruses it is small about 17 to 25 mμ in diameter In nature the virus is pantropic in that it has viscerotropic and neurotropic characteristics Viscerotropism enables the virus to attack the liver kidneys and heart while neurotropism permits it to infect cells of the central nervous system The virus becomes more neurotropic and loses its viscerotropism almost entirely during long continued brain to brain passage through mice Prolonged passage of the virus in tissue culture has produced an attenuated strain 17D suitable for use as vaccine

Man is universally susceptible to the virus and the characteristic symptoms and lesions of yellow fever in man are due to its viscerotropism severe disease being the exception rather than the rule The rhesus monkey while no more susceptible to infection by the virus is much more likely to die of the disease Albino mice especially of the Swiss strain are highly susceptible to the neurotropic element of pantropic strains of the virus provided they are inoculated by the intracerebral route

In urban yellow fever the *A aegypti* mosquito transmits the virus by biting a human host during his initial three-day period of viremia and later biting a susceptible person An extrinsic incubation

period of nine to twelve days must elapse before the mosquito becomes infectious by bite

In sylvan yellow fever man acquires his infection through the bite of some mosquito other than *A aegypti* In South America the virus has been isolated from wild caught mosquitoes of the genus Haemagogus and from *Aedes leucocelaenus* In Africa it has been obtained from wild caught *Aedes simpsoni* and *A africanus* The more important of these vectors Haemagogus and *A africanus* inhabit chiefly the forest canopy which is also the habitat of the monkeys which are most frequently infected in nature The exact role of monkeys in the epidemiology of sylvan yellow fever has not been elucidated

Since 1934 no large epidemics of urban yellow fever have been reported from the Western Hemisphere and the few small *A aegypti* transmitted epidemics which have occurred have been secondary to sylvan yellow fever In Africa in areas contiguous to the rain forest areas where sylvan yellow fever is endemic there are still frequent epidemics of urban yellow fever An important epidemic occurred in Nigeria in 1946 Beginning in 1948 in Panama an epidemic wave of sylvan yellow fever has been spreading northward through the forests of Central America

There is no evidence that yellow fever has ever been present in the Orient

Morbid Anatomy Yellow fever produces characteristic lesions in the liver of man There is necrosis and necrobiosis of the parenchymal cells most evident in the mid zones of the lobules with normal or much less involved cells around the central and portal veins The necrosis is scattered and irregular rather than massive and uniform Scattered among the necrotic cells are Councilman bodies parenchymal cells which have undergone eosinophilic hyaline necrosis There are also fatty changes in the parenchymal cells The liver lobules are not collapsed

Clinical Manifestations The great majority of attacks of yellow fever are mild and show few of the classic symptoms Not infrequently the only symptoms are low fever and headache both of short duration

The incubation period is from three to six days The onset is sudden often with a chill and without prodromal symptoms The first stage of the disease which lasts about three days is the *period of infection* The symptoms are fever severe headache backache pain in the legs and prostration The face is flushed and the eyes are injected there is photophobia The tongue is bright red at the tip and edges There is no jaundice at the onset of the illness The temperature rises abruptly to about 104° F sometimes higher The pulse may rise to 90 or 100 initially only to become increasingly slow in relation to the temperature (Faget s sign) The pulse is full and strong during this stage Nausea and vomiting are the rule as are epigastric distress and tenderness Constipation is to be expected A progressive leukopenia sometimes pronounced has frequently been observed early in the disease The sudden development of intense albuminuria about the third or fourth day is characteristic

After a short remission the *period of intoxication* begins about the fourth day The remission in fever is often indefinite or absent and it may be accompanied by a deceptive temporary improvement In this period lassitude and depression may replace restlessness and agitation Headache may diminish and jaundice gradually develops While jaundice is always present in severe cases it is usually not so marked as the name of the disease would indicate The gums are swollen and bleed easily either spontaneously or when pressed the nose may bleed There may be petechiae in the skin Hemorrhages from the stomach intestine or uterus or subcutaneously may be massive The pulse rate falls progressively and may go below 50 per minute Even in otherwise mild attacks there may be marked dilatation of the heart and low blood pressure as evidence of myocardial damage Vomiting may be frequent and distressing and the vomitus in this stage usually contains altered blood The amount of albumin in the urine rises often to 3 to 5 gm per liter sometimes much higher Fatal cases often exhibit hiccup copious vomiting of altered blood tarry stools and anuria Coma may last two or three days or death may be immediately preceded by a short period of wild delirium Death occurs most frequently from the sixth to the ninth day

When there is recovery from a severe case the temperature is likely to reach normal by the seventh or eighth day Convalescence begins then and progresses rapidly to complete recovery with rapid disappearance of the albuminuria Relapses do not occur and there are no sequelae Complications are rare A life long immunity follows the attack whether it be mild or severe

A peculiarity of yellow fever is the great variation in the degree to which different

organs are affected With much renal involvement there may be no cardiac symptoms and vice versa In mild and moderate cases there is little or no albuminuria jaundice or hemorrhage

Diagnosis In a severe febrile illness with black vomit intense albuminuria and jaundice yellow fever must be suspected Diseases which must be differentiated from severe yellow fever are infectious and serum hepatitis acute yellow atrophy of the liver carbon tetrachloride poisoning other jaundices and even malaria In mild cases of yellow fever which have been confused with dengue and influenza clinical diagnosis is notoriously inaccurate The necessary laboratory diagnostic procedures are highly specialized These are two the isolation of the virus in mice or rhesus monkeys and yellow fever neutralization tests on paired acute phase and convalescent serums

For postmortem diagnosis specimens of liver and other tissues should be preserved in 10 per cent formalin for histological examination

Prognosis Early in the disease the prognosis should always be guarded since sudden changes for the worse are not uncommon If early symptoms are mild rapid recovery is probable though some severe cases will end favorably Hiccup copious black vomit melena and anuria require a very grave prognosis

The over all average case fatality rate is less than 10 per cent and rates of less than 5 per cent have been observed in epidemics involving completely susceptible populations Rates as high as 85 per cent have been observed but they are most exceptional Even the often cited 50 per cent rate is false because large numbers of mild cases have been missed

Treatment There is no specific treatment A patient should be moved as little as possible and should be kept quiet in bed The severe headache and body aches may require relief with an analgesic The heart should be watched carefully throughout the illness and into early convalescence

Water should be given in adequate amounts parenterally if necessary Easily assimilated food should be given to the extent which the patient will tolerate Citrus fruit juices ad lib are a time honored prescription but milk in moderate quantities would appear to be much more useful to a damaged liver When vomiting has ceased and the temperature is down full diet may be given Full activity should be resumed only gradually

Prevention If a case of yellow fever is treated in a place in which vector mosquitoes exist the patient must be kept under a bed net or in a mosquito proof room during the first four days of his illness

Vaccination is essential for persons who intend to visit yellow fever endemic areas and for the people resident in such areas Two strains of living virus have been used extensively for human vaccination The *17D vaccine is prepared in chick embryos* and is given by subcutaneous inoculation At the Pasteur Institute of Dakar the technique of vaccination by scarification of the skin was developed using the neurotropic French strain suspended in gum arabic solution With either strain an effective immunity to yellow fever is regularly produced Severe reactions to the Dakar type of vaccine seem to be more frequent than are reactions to 17D Vaccination ordinarily gives protection in a week and the consequent immunity has been shown to last at least six years Communities infested with *Aedes aegypti* should protect themselves by exterminating that mosquito making use of the efficient methods now available An urban epidemic can best be stopped by mass vaccination of the population combined with a DDT spraying campaign

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Measles

(*Morbilli Rubeola*)

Definition Measles is an extremely contagious febrile disease of high morbidity characterized by rash and catarrhal inflammation of the eyes and respiratory tract It is principally a benign disease of children but may afflict with equal frequency persons of any age not previously attacked by its virus

History Although exanthems comparable to measles were described in Arabian writings as early as the tenth century Sydenham in the seventeenth

century was probably the first to distinguish the dis ease clearly from other infections The infectious nature of measles was first conclusively demon strated by Hektoen in 1905 in man to man trans mission experiments Convalescent serum was shown to be effective in the prevention of the disease by Nicolle and Conseil in 1918

Etiology Measles is caused by a virus of narrow host range which induces manifest disease only in man and monkeys Until recently the demonstration of measles virus has been definitively dependent upon inocu lation of human subjects or monkeys The discovery (Enders and Peebles 1954) that the virus is propagable in a variety of tissue cultures has received abundant confirma tion This convenient method has permitted recovery of virus from the blood and throat washings of patients with typical measles and the demonstration of specific antibody response to infection This significant lab oratory advance now provides for the first time techniques for the specific diagnosis of measles Isolation of the virus and demon stration of antibody are still the province of the special virus laboratory however and entail techniques which are not yet generally available

It is to be expected that knowledge of the epidemiology immunology and patho-genesis of measles will be expanded rap idly now that the etiological agent may be manipulated with relative ease

Incidence and Epidemiology Measles is a disease of cosmopolitan distribution en demic in all but isolated populations It may occur at any time of the year but most out *breaks are in the late winter and early* spring The disease recurs in epidemic cycles at two to three year intervals in most civilized communities which have been studied This epidemic periodicity is best explained as a result of the introduction of new susceptibles into the population by birth or ingress from other areas When the proportion of nonimmunes reaches a cer tain crucial concentration disease and co incident dissemination of virus may occur to produce an epidemic It is likely that virus is introduced from sources external to the involved population probably by incoming susceptibles there is no solid evidence of subclinical infection or a post infection carrier state with unmodified measles to suggest local persistence of virus in interepidemic periods Isolated communi ties such as the Faroe Islands (Panum) are infrequently attacked by measles at which times manifest illness appears in virtually all persons not previously infected In Greenland a country not known to have been invaded previously by the disease a recent epidemic resulted in overt measles in 99 9 per cent of the indigenous popula tion (Christiansen and others)

Throughout most of the world measles is a disease of children most adults possess acquired immunity Morbidity and mortal ity rates do not appear to be influenced by sex or race Case fatality rates are highest in children less than five years of age and are also relatively high in the aged Con genital infection has occurred

There is no evidence that the virus may vary in virulence in nature The oft cited and notorious virulence of the disease in primitive isolated or crowded populations may be explained as a corollary of (1) more prevalent infection of feeble and aged adults (2) poor environmental condi tions (3) inadequate medical care and (4) secondary bacterial infections Because measles virus *per se* rarely induces fatal disease it is evident that fatalities attrib utable to measles may vary in incidence according to the prevalence of bacterial pathogens and the resistance of the popula tion to their presence

Communicability Measles is one of the most contagious of infections Demonstra tion of virus in nasopharyngeal secretions is in accord with epidemiological evidence that infection is disseminated and acquired by the respiratory tract Close physical proximity or direct person to person contact is the usual requisite for infection but third person transfer has occurred

Immunity An unmodified attack of *measles usually confers lifelong immunity* Able observers have described apparently authentic instances of second or even mul tiple infections Definitive proof of recur rent infection with measles virus is lacking however because specific diagnostic labora tory tests have only recently become avail able Detailed study of a family subject to recurrent attacks suggests an hereditary de fect in the capacity to develop immunity in certain cases One such patient was found to be capable of antibody formation and electrophoretic analysis of the serum showed no deficit of gamma globulin Temporary immunity may be passively acquired by receipt of convalescent serum or gamma globulin derived from the pooled serums of human adults (see Treatment) Humoral antibody is demonstrable in patients con valescent from gamma globulin modified measles The low incidence of measles in early infancy (first six months) is attrib uted to transient protection by placentally transferred maternal antibody

Morbid Anatomy Pathological changes in fatal measles usually represent the compound effect of viral and secondary bacterial infection Bronchopneumonia is almost invariably present it is most frequently interstitial but may be lobular with purulent exudate within the alveoli More representative of the pathology of the uncomplicated viral disease are changes within the tonsillar nasopharyngeal and appendiceal tissue removed during the prodrome These changes consist of subepithelial round cell infiltration and the presence of large multinucleated giant cells (Warthin) The latter are so characteristic that skilled pathologists have predicted the development of rash from their presence in surgical specimens The lesions clinically apparent as Koplik s spots derive from inflammatory mononuclear cell infiltration of buccal submucous glands and necrosis of focal vesicular lesions of the mucosa Rash is the result of proliferation of capillary endothelial cells in the corium and the coincident exudation of serum and occasionally erythrocytes into the epidermis

Pathological Physiology No consistent or characteristic aberrations in physiology are observed with measles The transient hemoconcentration and albuminuria found with other febrile diseases may occur A normal total leukocyte count or leukopenia is observed throughout the febrile period Initially the leukopenia is occasioned by a decline in lymphocytes on the first day of fever subsequently granulocytopenia ensues as well The incubation period is characterized by neutrophilia and convalescence by a relative lymphocytosis A false positive serological test for syphilis may be observed

Hormone like Effects of Measles Infection Several striking physiological effects of measles although poorly understood mimic the influence of corticotropin or the adrenal corticosteroids These are transient suppression of the tuberculin reaction improvement in eczema and allergic asthma delay in wound healing and the induction of remissions in leukemia Hodgkin s disease and lipoid nephrosis Whether these effects are directly attributable to the virus or are hormonally mediated is not known

Symptoms Following an incubation period which averages eleven days measles becomes clinically manifest with symptoms of *fever malaise* myalgia and headache Within hours *ocular symptoms* of photophobia and burning pain are evidenced by conjunctival injection tearing and exudate in the conjunctival sac Concomitantly or soon thereafter *catarrhal inflammation of the respiratory tract* is manifested by sneezing coughing and nasal discharge Less commonly hoarseness and aphonia may reflect laryngeal involvement In this prodromal stage of one to four days duration petechial lesions of the palate and pharynx or tiny white spots on the buccal mucosa (*Koplik s spots*) may herald the appearance of skin rash The white lesions described by Koplik characteristically occur lateral to the molar teeth and typically are mounted on red areolae of injected mucosa which may coalesce to form a diffuse red background Not invariably present they constitute a valuable if not pathognomonic diagnostic sign The enanthem may involve other mucous membranes such as the vaginal lining It may overlap the subsequent appearance of the cutaneous rash by one to three days Rarely a transient erythematous exanthema may occur in the prodromal period

The *rash* of measles follows the prodromal symptoms by two to four days occasionally as late as seven days It first appears behind the ears or on the face as a blotchy erythema spreads downward to cover the trunk and finally is manifest on the extremities The hands and feet may escape involvement Initially the eruption consists of discrete reddish brown macules which blanch with pressure Subsequently these lesions become slightly elevated tend to coalesce and may develop a hemorrhagic nonblanching component The rash fades in the order of its appearance its disappearance about five days after onset is attended by a fine powdery desquamation which spares the hands and feet At its maximum the exanthema usually marks the termination of malaise and fever in the uncomplicated illness

The *fever* of measles is commonly of the typhoidal progressively rising type and falls by lysis It persists for about six days and frequently reaches 103° F In the adult fever may follow rather than antedate the catarrhal symptoms Throughout the febrile period productive *cough* and auscultatory evidence of bronchiolitis may be evident These manifestations may persist after defervescence and cough is often the last symptom to disappear It is probable that bronchopulmonary symptomatology is an integral part of the primary viral infection roentgenographic evidence of pulmonary involvement is frequently seen in the uncomplicated disease in the absence of leukocytosis and obvious bacterial infection

Complications It is difficult to distinguish between those complications directly at

tributable to the virus of measles and those resulting from secondary bacterial infections The persistence or recurrence of fever and the occurrence of leukocytosis are presumptive evidence of the usual bacterial sequelae of *otitis media* or *bronchopneumonia* Beta hemolytic streptococci are the most frequent secondary invaders but pneumococci or influenza bacilli may be implicated The incidence of bacterial complications is increased by crowding debility and the prevalence of bacterial pathogens in the population Bacterially engendered sequelae may be unduly frequent in crowded contagious disease hospitals

Serious complications directly related to the measles virus are rare *Laryngitis* of sufficient severity to embarrass respiration has been observed and may warrant tracheotomy *Electrocardiographic abnormalities* may be found in as many as 30 per cent of children but clinical evidence of cardiac disease is meager in such cases *Abdominal pain* or *diarrhea* may be related to invasion of lymphoid tissue of the appendix or Peyer s patches These symptoms may lead to unnecessary surgery before the appearance of the typical rash

A rare (0 01 to 0 5 per cent) but serious consequence of measles is a demyelinating *encephalomyelitis* which may appear from one to fourteen days after the onset of infection This complication is associated with a recurrence of fever and headache vomiting and stiff neck Stupor and occasionally convulsions follow Localizing neurological symptoms may or may not be present Death ensues in about 10 per cent of patients about half of survivors suffer permanent residuals of varying severity (see chapter on Postinfection Encephalitis)

Other late sequelae of measles are thrombocytopenic purpura and exacerbation or activation of pre existing pulmonary tuberculosis

Measles Modified by Antibody Administration Attenuation of the natural disease by antibody prophylaxis may result in an illness of lessened severity comparable with the milder infection of the maternally immunized newborn Fever alone may be observed but some degree of xanthema is usually apparent Koplik s spots may not appear In general the course is truncated and relatively uncomplicated

Diagnosis The experienced layman can diagnose typical measles The querulous bleary eyed child his face blotched and his nose crusted with exudate presents a characteristic if miserable picture as he breathes open mouthed between paroxysms of sneezing and coughing The severity of the catarrhal symptoms distinguishes the disease from other eruptive fevers In the prodromal period the diagnosis should be suggested by (1) fever higher than that of the usual common cold (2) known measles in the community and (3) Koplik s spots on the buccal mucosa

Differential diagnosis (see table) in



Fig 2 *a* Early measles eruption (Reproduced from Therapeutic Notes by Courtesy of Parke Davis & Company)

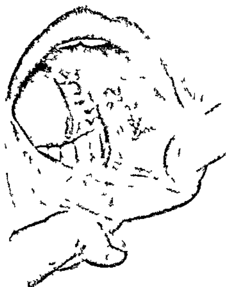


Fig 2 *b* Koplik s spots in measles (Hecker Trumpp and Abt)

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Complications It is difficult to distinguish between those complications directly at

beta hemolytic streptococcal infections These circumstances include treatment of the chronically ill the very young or the aged and the treatment of patients under crowded conditions which foster the increase and dissemination of pathogenic bacteria as may occur in contagious disease hospitals If careful observation of the patient is possible rational therapy is based on the prompt recognition and etiological definition of complications followed by initiation of the appropriate antimicrobial drug in proper dosage

Prevention No vaccine is yet available for the production of effective active immunity (see Treatment)

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Rubella

(*German Measles*)

Rubella is an apparently benign but potentially malignant infection of children and young adults This mild disease usually manifest only by its pale pink rash and posterior cervical lymphadenitis is now recognized as an important factor in the genesis of certain fetal abnormalities Accordingly recognition and prevention of the disease are matters of far reaching consequence

Etiology The causative agent of rubella is considered to be a virus largely on the basis of its filterability Study of the virus has been limited by its restricted host range its presence is demonstrable only by infection of humans or monkeys (Habel) The virus is detectable in both blood and nasopharyngeal washings soon after the rash appears and may be found in the blood two days before the eruption (Krugman and others) Nasopharyngeal washings may retain infectivity for as long as two years when stored at —70° C (Anderson 1950)

Incidence and Epidemiology Accurate information on the incidence of rubella is not available The mildness and brevity of its clinical signs may confound the diagnosis and reporting of many instances of infection Studies of the experimental disease lend support to prior clinical evidence that infection may occur without rash and indicate a further diagnostic pitfall It can be said however that the disease is seen on every continent may occur in epidemic form and has its highest incidence in the early spring The disease is less frequently acquired in childhood than measles as is attested by the fact that rubella is more common than measles in young adults The higher incidence of infection in younger age groups in institutional outbreaks argues against a greater susceptibility of the adult It is probable that rubella is spread by the respiratory route by close personal contact The infection is contagious during the period of prodromal symptoms and the first day of rash Like measles rubella rarely occurs in the first six months of life and is uncommon beyond the age of forty

Immunity is lasting Authenticated second attacks are rare and are virtually unprovable because of the nebulous nature of the clinical syndrome Passive immunity of questionable efficacy may be conferred by the injection of gamma globulin from the serums of patients convalescent from the disease (see Treatment) Rubella has no immunological relationship to measles

Morbid Anatomy Death from uncomplicated rubella is unknown Histological changes characteristic of the disease have not been demonstrated The onset of disease is attended by leukopenia resulting from a decrease in both lymphocytes and neutrophils After five days absolute lymphocytosis is manifest The total leukocyte count is normal at the tenth day

Necropsies of fetal and infantile victims of maternal infection have shown a variety of embryonal defects related to developmental arrest involving all three germ layers Those defects most consistently associated with maternal rubella are microcephaly cataract patency of the ductus arteriosus and defects of the interventricular septum Limited evidence suggests that agenesis of the organ of Corti underlies the deafness observed in affected infants

Symptoms Fourteen to twenty-one days after exposure to the infection the onset of rubella is evidenced by symptoms variable

A Guide to the Differential Diagnosis of Measles

	CONJUNCTIVITIS	RHINITIS	SORE THROAT	ENANTHEM	LEUKOCYTOSIS	SPECIFIC LABORATORY TESTS AVAILABLE
Measles	++	+	0	+	0	+
Rubella	±	±	±	±	0	0
Exanthem subitum	±	±	0	0	0	0
Scarlet fever	±	±	++	0	+	+
Infectious mononucleosis	0	0	+	0	±	+
Drug rash	0	0	0	0	0	0

0 not usually present no test available
± variable in occurrence
+ present test available
++ present and severe

cludes consideration of rubella scarlet fever exanthema subitum infectious mononucleosis secondary syphilis and drug eruptions Of value in excluding these possibilities are the milder course and pinker rash of rubella the sore throat and leukocytosis of scarlet fever and serological tests for infectious mononucleosis and syphilis The rash of exanthema subitum does not appear until the termination of fever Fever enanthema and catarrh are uncommon with the cutaneous manifestations of drug hypersensitivity

Specific laboratory diagnosis is still a research procedure (see Etiology)

Prognosis Uncomplicated measles is rarely fatal and complete recovery from the disease is the rule Fatalities are almost always the result of secondary streptococcal or pneumococcal pneumonia occurring principally in children below the age of five who become infected after the dissipation of passive neonatal immunity Case fatality rates are also high in elderly and tuberculous patients Cardiac decompensation is a common cause of death in patients over fifty years old

The introduction of antimicrobial drugs effective against the usual secondary invaders has reduced the case fatality rate of measles sharply in recent years The incidence of otitis media and pneumonia may be lowered by the prophylactic use of penicillin or a tetracycline early in illness

Encephalitis occurs as frequently in mild as in severe measles However modification of measles by gamma globulin prophylaxis (see below) affords an improved prognosis with reference to the encephalitic complication

Treatment There is no specific treatment for the fully developed disease The administration of convalescent serum or gamma globulin during the period of incubation may prevent or modify the manifestations of illness The degree of modification obtained is dependent upon the quantity of antibody given and the time of its administration In children of less than six years the intramuscular injection of 0 025 ml of gamma globulin per pound in the first half of the incubation period results in disease of lessened severity Two to four times this amount will prevent disease in nearly 80 per cent of children In older children and adults one and one half to two times as much globulin is recommended In young or debilitated children the aim is complete prevention of disease In children over five less subject to complications the goal of prophylaxis is attenuation of the infection sufficient to lessen symptomatology but not the development of effective immunity However recent studies indicate that recurrences of measles may follow the gamma globulin modified disease in contrast to the solid permanent immunity conferred by the unaltered natural infection

Symptomatic Therapy In the absence of complications bed rest is the essence of treatment in this benign self limited disease Codeine sulfate (0 015 to 0 06 gm) is useful in the amelioration of headache and myalgia and is effective in the management of cough Acetylsalicylic acid (0 3 to 0 6 gm) may be employed for its analgesic and antipyretic actions Diet should be unrestricted Bright light is not an ocular hazard but photophobia may require darkening of the patient s room

Antimicrobial Prophylaxis The course of uncomplicated measles is not influenced by antimicrobial therapy In common practice the incidence of serious bacterial infections is not sufficient to justify the routine prophylactic use of antimicrobials Certain special circumstances may warrant full therapeutic dosage with penicillin or the tetracyclines in anticipation of the potentially fatal sequelae of pneumococcal or

gamma globulin have been equally disap pointing prophylactic injection of suscep-tibles fails to protect them from the experimental disease *Nevertheless women exposed to rubella in early pregnancy should receive the benefit of gamma globulin pro phylaxis (as recommended for measles) despite its ambiguous status* In natural epidemics an equivocally significant pre ventive effect has been noted

Effective active immunization may be induced only by natural or experimental in fection The experimental infection is con tagious (Krugman and others) and consti tutes a potential hazard to pregnant women in the community Deliberate exposure of prepuberal girls to the natural disease has been practiced and is a reasonable measure in view of the mildness of the disease

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Cytomegalic Inclusion Disease

The term cytomegalic inclusion disease has been applied to a wide variety of in fantile clinical syndromes associated with the finding of enlarged epithelial cells bear ing intranuclear and cytoplasmic inclusions in salivary glands liver spleen lungs and other viscera Most cases are recognized only post mortem and thus comprise a pathological rather than a true clinical en tity Recently salivary gland virus has been recovered ante mortem from the viscera of infants in whom typical cytomegalic in clusions were also demonstrated The fact that this virus induces similar inclusions in tissue culture and that it is neutralized by the serum of infected children suggests the probable relation of the salivary gland virus to cytomegalic inclusion disease Limited studies with this newly recognized virus indicate that latent infection with the agent is widespread and that asympto matic virus carriage and excretion may occur for many months in young children

It is probable that a transplacentally ac quired fulminant disease of the newborn associated with hepatosplenomegaly and hemorrhagic diathesis is a severe manifes tation of cytomegalic inclusion disease Pri mary pulmonary disease in the form of interstitial pneumonia is less certainly a form of the disease while an apparent as sociation of the characteristic cellular in clusions with a variety of debilitating dis eases may represent only a secondary re activation by other processes of infection with salivary gland virus

No specific treatment for the disease is known Some patients with severe illness have survived The demonstration in many adults of antibody to salivary gland virus suggests that cytomegalic inclusion disease may be benign in most cases

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Herpes Simplex

(Herpes Febrilis Fever Blisters Cold Sores)

Definition Herpes simplex is an acute in fectious disease of man characterized by the development in the skin or mucous membranes of groups of superficial vesicles containing clear fluid

Etiology Herpes simplex is caused by a virus With the exception of herpes zoster all herpetic eruptions are thought to be in duced by the same virus This agent is of medium size and is 100 to 150 $m\mu$ in diam eter There are two types of herpetic dis ease (*a*) *primary* infections in persons without antibodies and (*b*) *recurrent* at tacks in persons with antibodies who are believed to be carriers of the virus The virus is capable of infecting the central nervous system of various experimental animals and humans

Morbid Anatomy Hyperplasia of epithe lial cells and necrosis and the development of vesicles containing clear fluid are the alterations usually seen in affected tissues

in their occurrence and severity Cough sore throat and coryza may initiate the ill ness but are often absent headache mal aise and myalgia may precede the eruption especially in young adults Commonly fever and obvious enlargement of posterior cer vical nodes antedate the appearance of the rash Fever when present rarely ex ceeds 101 F and seldom persists beyond forty-eight hours Injection of the bulbar conjunctivae may be noted Palpable tender and occasionally visible lymphadenopathy involves postauricular and suboccipital nodes with sufficient frequency to be an important diagnostic sign Generalized pe ripheral lymphadenitis and more rarely splenomegaly may occur

The exanthema of rubella is usually ap parent within twenty four hours of the first symptoms as a faint macular erythema which first involves the face and neck Characterized by its brevity and evanes cence it spreads rapidly to the trunk and extremities sometimes leaving one site even as it appears at the next The pink macules which constitute the rash blanch with pres sure and rarely stain the skin Diffuse erythema on the second day of rash may closely simulate scarlet fever The eruption has vanished by the third day Rubella may occur without rash An enanthema has been described which is inconstant in form and occurrence and lacks the premonitory sig nificance of the Koplik spots of measles The lesions consist of red macules which usually involve the soft palate

Complications Recovery is almost always prompt and uneventful although relapse occurs with greater frequency than with most viral diseases (5 to 8 per cent) Sec ondary bacterial infections rarely occur Rare complications are arthralgia neuritis gingivitis thrombocytopenic purpura and increased capillary fragility Heart block has been described A meningoencephalitis of short duration may occur one to six days after the appearance of rash Its incidence is estimated at 1 in 6000 cases and it is fatal in approximately 20 per cent of those afflicted

Embryopathic Effects The importance of rubella attaches to the well substantiated observation of Gregg that the occurrence of certain fetal abnormalities may be corre lated with a history of maternal infection in the first trimester of pregnancy Infec tion of the mother may lead to intrauterine fetal death or stillbirth or more commonly to delivery of a viable infant of small size Such infants show retardation in mental and physical development and varying de grees of congenital abnormality The na ture of the congenital defects observed has been related to the time of onset of the maternal infection and time of active proliferation of the primordia of organs subsequently manifesting defects Clinical manifestations in the infant may range in severity from dental hypoplasia to complete or partial blindness deafness and acyanotic cardiovascular disease Blindness is usu ally related to cataract deafness is of the inner ear type and patent ductus arteriosus is the most frequently observed cardiovas cular abnormality The latter condition has been related epidemiologically to the occur rence of rubella in contrast to other con genital cardiac defects

Original estimates of the incidence of congenital lesions following rubella were retrospective and therefore biased in the direction of finding a high rate of occur rence Recent prospective studies of preg nant women suffering rubella in the first trimester of pregnancy suggest that such women have a 90 per cent chance of giving birth to a normal baby

Diagnosis Rubella may be diagnosed with assurance only during an epidemic It may be difficult to distinguish from mild or modified measles infectious mononucleosis or scarlet fever Distinction from measles may be made on the basis of the pinker nonstaining rash the milder course and the lesser catarrh of rubella Sore throat is a more prominent complaint in scarlet fever the course of infectious mononucleosis is often more protracted and splenomegaly is more frequent than in rubella Definitive diagnosis of scarlet fever and infectious mononucleosis may be made by laboratory means No specific laboratory test is avail able for the diagnosis of rubella

Prognosis Complete recovery from ru bella is almost invariable The rare deaths attributable to rubella follow the infrequent complication of meningoencephalitis In fection in pregnancy constitutes a hazard to the fetus but not to the mother

Treatment There is no specific treatment for the disease Few patients suffer discom fort severe enough to warrant symptomatic medication Headache and myalgia may be controlled by acetylsalicylic acid bed rest is advisable for the duration of the fever

Prevention In contrast to measles cur rent evidence is conflicting with regard to the prophylaxis of rubella with convalescent serum and gamma globulin Various lots of gamma globulin appear to vary in prophy lactic potency some being completely in effective Trials of convalescent serum

these tests antibody appeared in zoster and varicella convalescent serum to an almost identical degree and appeared to establish the identity of the viruses from each syndrome The antibodies appear within four to seven days after onset and reach a peak in about three weeks with a subsequent slow decline The agents cause focal cytopathic changes that are associated with intranuclear inclusion bodies in tissue cultures

The portal of entry of the virus in zoster is unknown It is not certain how it reaches the ganglia it affects The occurrence of so called symptomatic herpes zoster in association with various pathological processes about the ganglia *e g* tuberculosis syphilis or neoplasms suggests that the agent may either be present commonly in the environment or often latent in human tissues

The portal of entry in varicella appears to be the upper respiratory tract Varicella may be regarded as the early generalized infection with the virus and zoster is a late localized manifestation in the immune or partially immune person at a later age period

Morbid Anatomy In zoster the basic lesion is in the dorsal root or extramedullary cranial nerve ganglia corresponding to the sensory innervation to the areas of herpetic eruption The lesions consist of severe inflammation and destruction of ganglion cells and fibers

The cutaneous vesicle of zoster and varicella is situated in the epithelial layer and there is marked inflammation of the corium Acidophilic intranuclear inclusions are found in epithelial cells about the vesicle

Symptoms In varicella the incubation period is usually fourteen to sixteen days although it may occasionally be as long as twenty-one days Approximately twenty four hours after the onset of fever crops of vesicles followed or accompanied by vesicles with surrounding erythema appear on the face and trunk spreading usually to the mouth pharynx and extremities In chickenpox the lesions are usually most abundant over the trunk while the face and extremities suffer the most damage from smallpox Occasionally the generalized eruption will be accompanied by a localized eruption characteristic of zoster The eruption occurs simultaneously with the fever and its duration is proportional to the height and persistence of the fever Successive crops of lesions appear furnishing all of the characteristic stages of papules vesicles and crusts at the same time over the affected areas There is general lymphadenopathy which is particularly noticeable in the suboccipital and the posterior cervical regions when vesicles occur in the scalp The vesicles which are indistinguishable from those of zoster frequently become pustular and the crusts are often removed by scratching because of the itching Impetigo furuncles septicemia and glomerulonephritis may complicate the picture Vesicles on the laryngeal mucosa about the eyes and genitalia and in the hair present difficult problems The encephalitis which occasionally complicates varicella is symptomatically similar to that accompanying zoster but is less common and less severe than that occurring in measles Occasionally neuritis of the cranial nerves or myelitis may occur Even temporary blindness may complicate the picture Pneumonitis occurs in very severe or fatal cases particularly in adults and radiologically presents a characteristic bilateral nodular infiltration A fatal nodular pneumonitis has been occurring more recently in persons who have contracted varicella while receiving steroid therapy which greatly diminishes resistance Small depressed white scars on the skin may result from severe varicella and from scratching with secondary infection

In cases of so-called idiopathic herpes zoster a typical attack rises without any obvious cause There is a prodromal period usually of three or four days duration during which the patient feels ill the temperature is elevated and there is more or less pain At this time a definite diagnosis cannot be made but suddenly the erythematous and vesicular eruption appears with its characteristic distribution along the course of a sensory nerve usually of the trunk occasionally in a trigeminal area The eruption is frequently preceded or accompanied by enlargement of the regional lymph nodes There is often an increase in the number of cells in the cerebrospinal fluid

The febrile period lasts usually from three to five days and with its subsidence drying and healing of the cutaneous lesions take place Secondary infection may delay healing and increase the tendency to scratch Neuralgic pains may persist especially in elderly people and rarely there is some local residual paralysis

Herpes zoster of the face occurs and is often severe It usually results from involvement of the first branch of the sensory division of the trigeminal nerve and may lead to serious corneal ulceration which requires

Inflammation in the adjacent corium is associated with these changes Infected cells often show nuclear inclusion bodies

Incidence Herpetic eruptions often develop without evident cause and in the absence of other pathological conditions Frequently they occur during the course of *various infectious diseases such as pneu*monia cerebrospinal meningitis malaria diphtheria and so forth In some persons recurrent herpes is seen and in women it may be associated with menstruation Injections of foreign proteins vaccines or fever therapy may precipitate an attack of herpes

Symptoms Primary infections common in young children are associated frequently with vesicular gingivostomatitis and may produce a constitutional reaction with fever irritability malaise and local lymphadenopathy The disease is self limited but symptoms may persist for seven to ten days

Recurrent attacks common in adults usually are associated with herpetic eruptions which may occur anywhere in the skin or mucous membranes Common sites are the lips face mouth genitalia conjunctiva and cornea The lesions at first cause small painful swellings that rapidly develop into vesicles surrounded by areas of erythema The vesicles are usually filled with clear watery fluid but suppuration may ensue At times particularly in the skin of the face the distribution of lesions is similar to that seen in herpes zoster Recurrent herpes simplex is usually a mild local lesion when it is not associated with another infectious disease general symptoms are rarely encountered

Prognosis In the absence of secondary infection the herpetic eruption gradually recedes and disappears Corneal herpes may cause serious scarring and impairment of vision One attack does not confer immunity against subsequent attacks

Treatment No specific treatment has been developed Local applications may relieve pain and swelling but do not shorten the course of the eruption

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Varicella, Herpes Zoster

(*Chickenpox Zona Zoster Shingles*)

It has become apparent that these diseases may be considered as two syndromes resulting from the activity of a single virus of uniform antigenic composition without known strain differences They thus may be described as two phases of a single disease

Definitions *Varicella* is a mild communicable disease or syndrome confined chiefly to children It is characterized by fever and an itching vesicular eruption of the skin and mucous membranes individual lesions of which are surrounded by erythema *Herpes zoster* is an acute infectious syndrome *characterized by inflammation of* one or more dorsal root ganglia or extramedullary cranial nerve ganglia It is associated with a painful vesicular eruption in the skin or mucous membranes which is distributed along the course of peripheral sensory nerves arising in the affected ganglia

History Barensprung (1863) showed that zoster is associated with inflammation of the corresponding dorsal root ganglion Head and Campbell (1900) made a classic study of the neuropathology Bokay (1909) suggested that zoster and varicella are related etiologically Kundratitz (1925) reported successful attempts to transmit zoster to human beings and also produced varicella by this means Weller (1953) propagated the etiological agent in cultures of human tissues

Etiology Present evidence strongly suggests that herpes zoster and varicella are caused by the same virus The agent has been serially propagated *in vitro* in cultures of human tissue Viral bodies from vesicles of varicella and zoster are brick shaped and identical in appearance and size (210 to 250μ) Vesicles twelve hours old contain numerous viral particles but those twenty four hours old yield very few Roller tube cultures of virus from both varicella and zoster by Weller have permitted antigenic analyses by complement fixation neutralization and fluorescent antibody tests In

rial from active lesions or variola crusts for transmission of the disease with a view to controlling it marks the first use historically of any active virus in planned transmission The use of crusts or pustular lesions was later replaced by the use of fluid from early vesicles for scarification of human susceptibles The resulting disease resembles varioloid (modified smallpox see below) in that a local lesion occurs at the point of scarification followed in about eleven days by a mild generalized eruption which usually leaves no scars Variola virus generally produces a mild disease similar to varioloid in anthropoids and in monkeys it may occur by contact simultaneously with a human epidemic

Transmission of smallpox to susceptibles may occur during all stages of the disease and until the scabs have disappeared The disease apparently spreads principally by the air borne route Dry desquamated crusts dust and bedding of a patient s room as well as letters may remain infective for long periods and thus inhalation of the air from a patient s room may at times account for infection

Occurrence of small outbreaks of smallpox even among the carefully vaccinated U S Army has demonstrated the need for vaccination in the presence of epidemics For example in 1945 and 1946 the U S Army in Korea suffered 121 cases of smallpox with 25 deaths Revaccination of troops in this area with fresh vaccinia virus completely controlled the outbreaks which however continued among the nonmilitary population

The incidence of smallpox has been greater in the United States where vaccination is not nationally compulsory than in countries which require vaccination In the United States the incidence is particularly high in those states which make little effort to vaccinate children against the disease but cases have been occurring in every state In Philadelphia there were 2585 deaths from smallpox in 1872 and as late as 1904 over 200 deaths occurred yearly with the advent of compulsory vaccination no deaths from smallpox have occurred since 1924

Smallpox is more frequently fatal in infants and children No transplacental immunity appears to be established—a situation similar to that of varicella Smallpox contracted during pregnancy may involve the fetus and infants have been born suffering from a typical eruption Pregnant women suffering from a severe attack of the disease usually abort Men and women are equally susceptible Complete natural immunity is extremely rare but permanent immunity is generally established by a single attack since there have been only a few reports of second attacks

There appears to be a greater susceptibility among the colored races to the virus of smallpox Although smallpox generally occurs during the winter months this is probably due to closer contacts within inclosed spaces in the colder weather Epidemics have been known to occur during the summer weather There is a great variation in the severity of epidemics and fortunately those of recent years have been mild This may be the result of greater emphasis upon cleanliness of the skin with resultant diminished danger of secondarily invading bacteria The virus itself also appears to vary in virulence and many mild cases termed *varioloid* may occur Such mild cases in the majority of instances appear to be a result of previous vaccination On the other hand the virus appears at times to gain in virulence as the epidemic progresses

Morbid Anatomy The pathological lesions are almost entirely in the skin and mucous membranes The lack of a cornified epithelium in the mucous membrane prevents the development of a typical vesicle and pustule while ulcers with a deep crater and a surrounding red areola are common similar to those of varicella but usually more extensive These ulcers often occur in the buccal and nasopharyngeal mucosa larynx trachea esophagus vagina and even in the intestinal mucosa at times The bladder ureters and urethra are rarely involved Secondarily invading streptococci and staphylococci frequently are present and increase the severity of the disease but the pustular stage of the eruption occurs irrespective of the presence or absence of these organisms The local skin lesion is a multilocular pock in which the epithelium becomes degenerated and vacuolated with transudation of serum and the formation of a reticulum As the reticular spaces swell with transudate and later with exudate their walls rupture to form the typical pustule This pustule may be only in the epidermis but frequently extends into the corium Such lesions contain both the typical cytoplasmic acidophilic inclusions lying close to the cell nucleus termed the Guarnieri bodies and also the intranuclear inclusions A single cell apparently does not include both types of inclusions *i e* both cytoplasmic and intranuclear The round or oval Guarnieri body which is about 10

special care The other cranial nerves are rarely affected

Diagnosis In zoster because of the characteristic sensory nerve distribution of the vesicular eruption the diagnosis is usually not difficult after the lesions appear In children and rarely in adults the local eruption may be followed by the appearance of numerous other vesicles apparently unrelated to cutaneous innervation

Occasionally the virus of herpes simplex causes a vesicular eruption along the course of a cutaneous nerve usually limited in extent and it may involve the supraorbital branch of the ophthalmic nerve This may closely simulate a mild herpes zoster In such cases the presence of the virus of herpes simplex can be demonstrated in laboratory animals The viruses of herpes zoster and of varicella on the other hand are transmissible only to man or cultures of human tissue Immunological techniques have been developed for determining the presence of antibodies against the viruses These may become useful in diagnosis Varicella and zoster are frequently indistinguishable The severe constitutional reaction caused by smallpox with a drop in fever as the rash appears together with uniformity of development of the eruption in all areas of the skin at the same time and the somewhat larger number of vesicles on the extremities as compared with the trunk serve to distinguish this disease from varicella Also in smallpox the lesions tend to be deeper shotty and umbilicated

Treatment There is no specific treatment in zoster Relief of pain and prevention of secondary infection of the surface lesions are the most important considerations In mild cases salicylates or codeine is sufficient but in severe cases morphine or Demerol may be required to relieve pain Locally antiseptic powders or ointments containing phenol cocaine and the like may be used Numerous special remedies have been offered *e g* paraffin coating ultraviolet irradiation x ray therapy certain antimicrobial drugs and so on but there is no convincing evidence that any of these procedures is of value In so-called symptomatic herpes zoster treatment should be directed to the cause of the associated condition *i e* syphilis tuberculosis tumor and so forth

Postherpetic neuralgia may be prolonged and refractory to treatment In patients who suffer intractable pain posterior root section or ganglionectomy may be necessary For children with varicella cutting and cleaning the fingernails are important

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Smallpox

(*Variola*)

Definition Smallpox is an acute communicable disease characterized by severe constitutional symptoms and a single crop of skin lesions all proceeding at the same rate through a macular papular vesicular and pustular stage over a period of approximately three to ten days

History In addition to certain evidence in the earliest records of China and Egypt suggesting its presence in both Asia and Africa the disease undoubtedly changed the course of the Roman Empire and later altered the course of history among nations kings and men of all nationalities throughout Europe and the British Isles up to the time of Jenner In the Western Hemisphere the conquest of the natives by the European races may be attributed in no small degree to the devastating effect of the introduction of the virus of smallpox among the Indians by their conquerors However the discovery of vaccination by Jenner dramatically altered the role of the virus from that of the conqueror to that of the conquered

Etiology and Epidemiology Smallpox is caused by a virus which in size and shape closely resembles the cuboidal or bricklike vaccinia virus These viruses can readily be grown on the chorioallantois of the embryonated egg and have a diameter of about 200 mμ They are readily stained by certain aniline dyes The virus of smallpox is found in the vesicular fluid being slightly larger than the varicella virus It withstands drying for long periods without refrigeration which probably accounts for the ease with which it is transmitted Both *in vitro* and *in vivo* tests have indicated the presence of common antigens and antibodies for both viruses

Variolation the practice of using mate

in diameter with an appearance unlike any other exanthematous disease Widespread tuberculids all of the same size and symmetrically distributed could have the same appearance With the increasing size and tenderness of the papules *multilocular vesicles* begin to form over the papules on about the sixth day characteristically umbilicated because of a dry and depressed center Some vesicles are superficial while others are deeper and not so readily recognized By approximately the eighth day the vesicle becomes full of cloudy fluid and the typical *pustular rash* is in full bloom The pustular nature of the lesion apparently is not dependent upon the presence of secondarily invading bacteria although they are often present and greatly increase the danger of complications The pustules are slightly larger than the papules with somewhat greater elevation and have a characteristic greenish or grayish yellow color A small red areola forms about each lesion at the time of vesiculation a phenomenon which occurs synchronously with the development of an allergic response of the skin to variolous material

Although the lesions may vary slightly in size they proceed through each stage of development at the same time and do not appear in crops as is characteristic of varicella with which otherwise mild smallpox might be readily confused Although all the lesions appear at approximately the same time a small percentage of them do not progress through all the characteristic steps but remain at times only as papules or with very slight evidence of vesiculation In such lesions involution occurs frequently in the earlier stage of the disease

The rash usually appears on the face and about the wrists only slightly in advance of its appearance on the rest of the body and then rather rapidly involves the rest of the forearms upper arms and thorax The lateral region of the neck from the clavicle to the lower jaw the inguinal areas and around the eyes usually have very few pocks The abdomen and legs are often only slightly involved but in severe cases this may not be true Such severe cases in which the rash is widespread and in which the lesions are so closely studded over the skin that they coalesce are termed *confluent* whereas in the absence of coalescence the term *discrete* may be used

Frequently these two forms confluent and discrete occur in the same patient the confluent lesions appearing on the face and about the wrists while the discrete lesions appear on the thorax abdomen and legs In certain confluent lesions the area involved has almost the appearance of a large abscess On the face these lesions can be particularly distressing often producing extreme discomfort edema may close the eyelids and involve the tissues of the neck as well Edema of the hands and feet often occurs in children At the height of the pustulation lesions frequently occur in areas which must be watched closely for secondary infection the mouth and nasopharynx the prepuce the labia and the vagina Lesions on the palms and plantar surfaces are not apt to develop into vesicles and pustules but nevertheless form crusts Marked pitting of the face or arms occurs as a rule only in the areas where the lesions are confluent

The pustules and crusts itch severely and scratching must be prevented Desquamation may begin at the twelfth to the fourteenth day Unlike the branny desquamation of measles and scarlet fever the desquamating crusts are thick and brownish yellow in appearance A dark blue discoloration of the skin occurs in the area from which the crust has separated but this gradually and completely disappears

Blood There is usually a leukopenia together with a relative mononucleosis in the earlier stages of the disease but later a leukocytosis occurs particularly during the pustular stage and when secondary complications occur Anemia usually occurs together with enlargement of both the spleen and the liver In the two hemorrhagic types of smallpox previously mentioned considerable depression of the bone marrow and the liver may occur resulting apparently in alterations in the platelets fibrinogen and prothrombin The exact origin of such hemorrhagic phenomena however is not entirely clear

Varioloid This term is usually applied to smallpox modified by a vaccination which has "taken successfully within approximately five years The lesions are of the discrete type the prodromal symptoms are rarely severe there is no secondary rise of fever and the lesions frequently undergo involution with a markedly shortened course

Abortive Types Occasionally in recently vaccinated persons early involution of the eruption occurs even before vesicles are well established and in rare instances the eruption never develops a condition which is known as *variola sine eruptione*

Complications The common complications of smallpox may be considered as largely due to the secondary invasions of



FIG 3 Smallpox in a young man during the active stage of the disease Note the even distribution of lesions on the face and trunk (Courtesy of Drs Vernon Knight and A Ruiz Sanchez)

microns in diameter with an unstained halo around it is probably a mass of variola virus imbedded in a matrix while the intranuclear inclusion apparently does not contain virus The latter is also round or oval somewhat smaller than the Guarnieri body is acidophilic and is separated from the nuclear membrane in histological preparations by an unstained halo

Two types of hemorrhage may occur with the lesions (1) *purpura variolosa* or black smallpox in which extensive hemorrhages invade the corium only occurring however in the most severe cases soon after the onset of the disease and usually fatal and (2) *variola haemorrhagica pustulosa* in which small localized hemorrhages occur into the pock—a severe form of the disease but causing fewer fatalities than purpura variolosa

Aside from the local changes in the cutaneous lesions of smallpox the general pathological picture as far as has been determined differs little from that resulting from other severely toxic states The lungs are frequently involved by secondarily invading organisms such as pneumococci and streptococci resulting in bronchopneumonia which may be hemorrhagic at times The liver is usually enlarged at the time the pustules develop and may also contain hemorrhagic foci The spleen is similarly enlarged during the pustular stage and hemorrhages may also occur into the pulp Because of the marked involvement of the skin of the face the cervical lymph nodes are also considerably enlarged chiefly with edema which extends beyond the capsule of the node The marrow is notable for the absence of polymorphonuclear elements and megakaryocytes and hemorrhages frequently occur in the more severe cases Hemorrhages also may occur into the pelvis of the kidneys and into the ureters usually beneath the mucous membranes and severe degenerative changes in the kidneys themselves are often noted

There is a characteristic proliferation in the hematopoietic system and extensive infiltration particularly in the liver kidney adrenals and testicle of mononuclear basophilic cells which in areas such as the testicle appear to cause pressure severe enough to produce occasionally localized necrosis

Symptoms *Clinical History* The *period of incubation* lasts usually from ten to fourteen days but may be somewhat shorter or longer In vaccinated persons a longer incubation occurs at times followed by milder disease which has been termed *variola minor* At onset the constitutional symptoms are severe with marked headache usually a chill or chilliness aching of the back and limbs quite similar to that of epidemic influenza and a mounting fever which may reach a height of 106° or 107 F In children convulsions and vomiting or drowsiness quickly followed by coma may occur The patient is usually prostrated the face is flushed the pulse is usually full and bounding and marked restlessness which at times amounts to delirium supervenes

Transient rashes resembling scarlet fever or measles may occur during the *prodromal stages* of the disease while the temperature is approaching or when it has reached its highest point Such rashes occur only during the first two days and are found usually over the lower abdomen and the inner aspects of the thighs The position of the rash and its lack of elevation serve to distinguish it from measles or scarlet fever At times such a rash ushers in the more severe types of smallpox

On the third or fourth day *raised macules* begin to appear over the face The earlier these macules appear the more likely is the rash to become confluent The macules rapidly develop into *papules* and with this development there is associated an immediate diminution in the severity of symptoms and the fever the patient becoming considerably more comfortable Fever and symptoms usually increase later irrespective of multiplication of staphylococci or streptococci in the pustules with their attendant complications The single crop of papules are firm and shotty 2 to 4 mm

in diameter with an appearance unlike any other exanthematous disease Widespread tuberculids all of the same size and symmetrically distributed could have the same appearance With the increasing size and tenderness of the papules *multilocular vesicles* begin to form over the papules on *about the sixth* day characteristically umbilicated because of a dry and depressed center Some vesicles are superficial while others are deeper and not so readily recognized By approximately the eighth day the vesicle becomes full of cloudy fluid and the typical *pustular rash* is in full bloom The pustular nature of the lesion apparently is not dependent upon the presence of secondarily invading bacteria although they are *often present and greatly increase the* danger of complications The pustules are slightly larger than the papules with somewhat greater elevation and have a characteristic greenish or grayish yellow color A small red areola forms about each lesion at the time of vesiculation a phenomenon which occurs synchronously with the development of an allergic response of the skin to variolous material

Although the lesions may vary slightly in size they proceed through each stage of development at the same time and do not appear in crops as is characteristic of varicella with which otherwise mild smallpox might be readily confused Although all the lesions appear at approximately the same time a small percentage of them do not progress through all the characteristic steps but remain at times only as papules or with *very slight evidence of vesiculation In such* lesions involution occurs frequently in the earlier stage of the disease

The rash usually appears on the face and about the wrists only slightly in advance of its appearance on the rest of the body and then rather rapidly involves the rest of the forearms upper arms and thorax The lateral region of the neck from the clavicle to the lower jaw the inguinal areas and around the eyes usually have very few pocks The abdomen and legs are often only slightly involved but in severe cases this may not be true Such severe cases in which the rash is widespread and in which the lesions are so closely studded over the skin that they coalesce are termed *confluent* whereas in the absence of coalescence the term *discrete* may be used

Frequently these two forms confluent and discrete occur in the same patient the confluent lesions appearing on the face and about the wrists while the discrete lesions appear on the thorax abdomen and legs In certain confluent lesions the area involved has almost the appearance of a large abscess On the face these lesions can be particularly distressing often producing extreme discomfort edema may close the eyelids and involve the tissues of the neck as well Edema of the hands and feet often occurs in children At the height of the pustulation lesions frequently occur in areas which must be watched closely for secondary infection the mouth and nasopharynx the prepuce the labia and the vagina Lesions on the palms and plantar surfaces are not apt to develop into vesicles and pustules but nevertheless form crusts Marked pitting of the face or arms occurs as a rule only in the areas where the lesions are *confluent*

The pustules and crusts itch severely and scratching must be prevented Desquamation may begin at the twelfth to the fourteenth day Unlike the branny desquamation of measles and scarlet fever the desquamating crusts are thick and brownish yellow in appearance A dark blue discoloration of the skin occurs in the area from which the crust has separated but *this gradually and completely disappears*

Blood There is usually a leukopenia together with a relative mononucleosis in the earlier stages of the disease but later a leukocytosis occurs particularly during the pustular stage and when secondary complications occur Anemia usually occurs together with enlargement of both the spleen and the liver In the two hemorrhagic types of smallpox previously mentioned considerable *depression of the bone marrow and the* liver may occur resulting apparently in alterations in the platelets fibrinogen and prothrombin The exact origin of such hemorrhagic phenomena however is not entirely clear

Varioloid This term is usually applied to smallpox modified by a vaccination which has taken successfully within approximately five years The lesions are of the discrete type the prodromal symptoms are rarely severe there is no secondary rise of fever and the lesions frequently undergo involution with a markedly shortened course

Abortive Types Occasionally in recently vaccinated persons early involution of the eruption occurs even before vesicles are well established and in rare instances the eruption never develops a condition which is known as *variola sine eruptione*

Complications The common complications of smallpox may be considered as largely due to the secondary invasions of

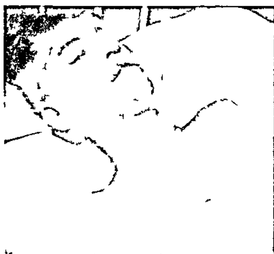


Fig 4 Same patient as in Figure 3 during convalescence after treatment with intravenous injections of oxytetracycline (Terramycin) for secondary invaders



Fig 5 Smallpox in an unvaccinated child showing distribution of eruption

staphylococci and streptococci Abscesses septicemia nephritis erysipelas laryngitis and the various lower respiratory infections can usually be traced to these organisms together with at times pneumococci Corneal ulcers and pustules of the eyelids are not uncommon Rarer though still important complications are diarrhea and otitis media in children and in adults hemiplegia encephalitis polyneuritis decubitus ulcers and gangrene

Diagnosis Difficulties in diagnosis arise chiefly from the following conditions

Varioloid with the involution of many of the lesions can be confused at times with varicella In such cases one must depend upon the appearance of varicella in crops of lesions in all stages of development and also upon the difference in distribution of varicella which is more plentiful on the trunk

The *severe hemorrhagic forms* can be confused with septicemia or severe meningococcal infection Blood cultures should establish the diagnosis

The *initial rash* which occurs in severe forms may be confused with that of measles or scarlet fever The short duration of the early evanescent rash of smallpox its distribution in the diaper area and the other accompanying symptoms should assist in differentiation

Pustular syphilids are at times extremely difficult to differentiate from smallpox In certain instances one can depend only upon the history and serological tests for syphilis for differentiation

The isolation of the virus on the chorioallantois of the embryonated egg has been quite successful inasmuch as pocks are produced by variola or vaccinia while material from lesions of varicella does not produce pocks Since differentiation from varicella presents clinical difficulties at times such isolation may be important The best method of diagnosis however is in the microscopic study of smears from the smallpox lesions in which the elementary bodies are readily distinguished

Prognosis The prognosis in smallpox depends largely upon the severity of the particular case In the epidemics of recent years the mortality has been distinctly lower than in the prevaccination era The

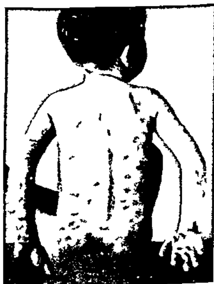


Fig 6 Same patient as in Figure 5 showing eruption on back and palms

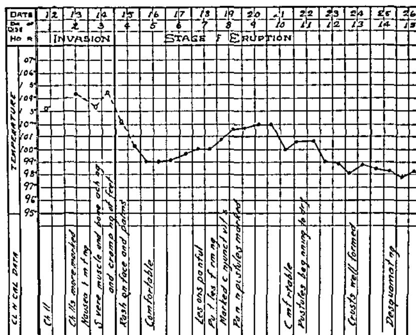


FIG 7 Typical temperature curve from a case of smallpox illustrating the secondary rise

cases accompanied by high fever are more likely to be fatal Complications particularly those in the respiratory tract add to the seriousness of the prognosis The mortality rate is greatest under five and over forty five years of age

Treatment The principal consideration in the treatment of smallpox is the prevention of secondary infection of the vesicles and pustules The secondary elevation of temperature which usually follows the appearance of the vesicles and pustules may depend partially upon the bacterial invasion of the lesions particularly by staphylococci and streptococci Treatment therefore should be aimed essentially as in varicella toward the prevention of itching and the cleansing of fingers the skin and garments or clothing which may come in contact with the lesions Also scrupulous care must be taken of the eyes nose and mouth in the more severe cases The advent of the sulfonamide drugs and penicillin has assisted greatly in the control of secondary infection of the lesions of smallpox Swabbing the lesions in wet dressings of potassium permanganate 1 4000 may prevent serious infection It is important that crusts should not be removed too quickly in view of the possible resultant scarring Bathing the lesions gently with hot water or antipruritic lotions should be done to alleviate the itching

Dehydration is a frequent severe complication of smallpox and should be avoided by rectal intravenous or hypodermic fluids particularly glucose if vomiting occurs The possible benefit of convalescent serum has not yet been determined The isolation period should be at least fourteen days and longer if the lesions remain in an active stage

Prophylaxis The problem of vaccination is considered properly in the article on Vaccinia Emphasis must be placed upon the fact that vaccination even during the incubation period of the disease may prevent its development Strict quarantine is essential

The disease is air borne as well as transmitted by contact or by direct droplet hits from the patient s nasopharyngeal secretions means of sterilization of the air must be considered as well as the prevention of close contacts and of spread by fomites

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Vaccinia

Vaccination or active immunization against smallpox by means of the virus of cowpox is the first procedure of this type known to medicine This discovery and development by Jenner long before bacteria or viruses had been identified is one of the most dramatic events of medical history The antigenic relationship of the vaccinia virus to cowpox and smallpox viruses is not clearly understood since in certain areas of the world the vaccinia virus appears to have derived from cowpox virus and in other areas from smallpox virus Whatever the derivation of the vaccinia virus apparently it has become antigenically stable and produces a characteristic pox lesion In view of the proved immunity produced by vaccination with vaccinia virus against smallpox these two viruses antigenically must be quite similar

Etiology and Epidemiology Vaccinia or cowpox virus has been studied as diligently and has received as adequate definition as any virus According to the definition of some workers it is cuboidal and according to others bricklike with a shape and size similar to those of the smallpox virus In purified preparations of the virus obtained from infected epidermal cells of a rabbit it has been determined by a variety of calculations that a single infective particle apparently will produce the lesion of vaccinia

When variolation is performed five days after vaccination only a local lesion results while at eleven days variolation produces no lesion Vaccination takes during the prodromes of smallpox but not when performed a few days after the eruption has appeared Serums obtained from cases of either vaccinia or variola neutralize both viruses

Malnutrition in rabbits has been shown to reduce the size of the vaccinial lesion Also methionine choline and estrogenic substances have reduced the susceptibility of rabbits to vaccinia The available antimicrobial drugs have shown relatively slight inhibiting effects on the vaccinia virus Storage with glycerol at 5 to 10° C and lyophilization have been adequate to maintain viral activity Ultraviolet light and x ray radiation inactivate the virus

The virus of vaccinia obtained from the contents of vesicles of vaccinated calves ordinarily has been preserved by dilution 1 5 in 50 per cent glycerin saline solution containing 1 per cent phenol As distributed in capillary glass tubes in the United States the presence of fewer than 50 nonpathogenic bacteria per dose is required by law At a temperature below 5° C the virus can be kept active for at least three months but it is readily inactivated at room temperature More recently it has been grown in tissue cultures by the methods of Rivers and Goodpasture which have almost entirely eliminated bacterial contamination These preparations can be used intradermally and produce a much milder reaction with a closed lesion Although the protection afforded against smallpox is probably as solid as that produced by the more usual material sufficient experience with its value in the face of an epidemic of smallpox has not been obtained to warrant its widespread use

Proper Age for Vaccination In view of the fact that severe reactions particularly the complication of encephalomyelitis are less apt to occur when vaccination is performed during the first year it is best to vaccinate an infant about the fourth to the sixth month The choice of months however should vary according to a number of factors It is essential that no fixed or invariable order of immunization procedures be followed in infants since epidemics of communicable diseases respiratory infections the convenience of the family and the physician the weather and other factors should all be considered in such procedures It is wise to avoid hot weather because of the possibility of a marked febrile reaction and to avoid vaccination within a certain period following illness and until the latter half of the first year in premature infants or those who have suffered from nutritional difficulties The presence of such cutaneous conditions as eczema impetigo and other skin diseases in the infant or in close contacts of the infant should cause postponement of vaccination until the skin is normal In chronic eczema or in other cutaneous conditions which are not readily curable however tissue culture virus injected by the intradermal method can often be used successfully with less danger of bacterial contamination

Choice of Site for Vaccination The area of choice for both sexes is the skin on the posterior and upper portion of the arm close to the axilla where the scar is not readily visible and where the friction is minimal

Method of Vaccination In the development of techniques for vaccination over many years the objective has been to produce a lesion which results in as inconspicuous a scar as possible but still

produces an optimal degree of immunity Although serological means of determining such immunity are not available experience in the presence of epidemics of smallpox and with the results of revaccinations has indicated that the take from the recent methods of vaccination resulting in a small scar may not be as highly protective as the "take" with the large scar or scars resulting from the older methods of vaccination Many physicians believe that scarification or drilling of a large area of skin and the resultant lesion are essential for a solid and more lasting immunity The danger of secondary infections from the larger lesions and the added discomfort and fever do not justify such a procedure except in the presence of epidemic or endemic smallpox when two to four separate areas of skin should be inoculated

The methods recommended at present are of three types (1) single scratch or incision method (2) drill method (3) multiple pressure method In these methods the objective is to permit the virus to enter the skin in as small an area as possible without sufficient trauma to draw blood The skin of the selected site should be cleansed thoroughly with sterile cotton and ethyl alcohol acetone or ether care being taken to avoid abrasions which might result in multiple "takes The site should also be permitted to dry thoroughly after cleansing in order to avoid inactivation of the virus The vaccine tube should remain in the refrigerator until immediately before use when the ends may be filed and broken off and the small rubber bulb attached for expressing the fluid

1 *Scratch or Incision Method* A single scratch 1/4 to 1/4 inch in length should be made in the skin with a sterile needle or point drawn through the drop of lymph More than one scratch may be made if the first appears to be insufficient but cross scratches should never be used The needle or point should then be placed horizontal with the skin and rubbed gently over the scratched area after which the drop of lymph should be rubbed off lightly with dry sterile cotton

2 *Drill Method* Multiple pricks are made through the drop of lymph with the needle held vertical to the skin surface The number of pricks should be limited to five or six and the lymph may then be wiped off with dry sterile cotton

3 *Multiple Pressure Method* The needle or point is held at an angle of approximately 45 degrees with the skin surface and is moved up and down rapidly with pressure on the skin sufficient to puncture it lightly six to ten times Erythema but no blood or serum should be noted after the procedure and the lymph may be wiped away immediately with sterile cotton as in the other methods In the youngest infants a greater number of punctures is advisable

In all these methods no dressing should be used but scrubbing the area with soap and water should probably be avoided for the following twenty four hours

Types of Reaction In general it may be said that the longer the incubation period the greater is the susceptibility of the vaccinated person and the more severe is the reaction The small sized reaction which occurs within the first twenty four to seventy two hours and disappears rather rapidly denotes a high degree of immunity whereas the usual "take" with the large reaction which begins to develop typical signs after five or six days and reaches its height at eight or nine days is evidence of a highly susceptible person Between these extremes of reaction and susceptibility there are many intermediate responses and degrees of immunity which follow a characteristic pattern

In order of degree of immunity which they indicate the following reactions can be classified approximately as follows

1 *Immediate or Immune" Reaction* This occurs as a papule with a light surrounding erythema usually reaching its height during the first three days after the inoculation and then receding rapidly in size and reactivity Persons showing this type of reaction often have been previously vaccinated within a relatively short time

Inactive virus as well as active virus can give an immune reaction although the former cannot produce immunity Thus unless vaccination is performed with the same material on a number of persons some of whom would have primary takes" or accelerated (vaccinoid) reactions one may be mistaken concerning the immunizing value of the vaccine material used

2 *Accelerated Reaction* In such persons the immunity is less than in the preceding type the reaction reaches its height in from three to five days and there is a vesicle rather than a papule with a marked erythema extending well out from the base of the vesicle The entire area rarely extends over 1/ to 3/4 inch in diameter Slight fever malaise chilliness aching local tenderness and slight enlargement of the draining lymph nodes frequently occur By some this type of reaction has been termed vaccinoid

3 Primary Vaccination Reaction or Typical Take In the typical take little is noted at the site of inoculation except for a punctate area of erythema until the fifth day when a vesicle appears with a rapidly increasing erythema and induration about it Usually the vesicle erythema and induration increase up to the ninth day when the total area involved ranges approximately from the diameter of a silver half dollar up to the diameter of a grapefruit or even at times beyond in adults The vesicle itself if the vaccination is properly performed rarely exceeds ¼ to ½ inch in diameter but the area of erythema and induration may not only extend in a wide circular areola but may reach out toward the draining lymph nodes to involve areas of skin many inches from the central vesicle In certain instances where primary takes have occurred by mistake on the tips of the fingers acute lymphangitis resembling that due to hemolytic streptococci may occur during the height of the reaction and extend well up the arm—apparently the result of the tension produced in such a restricted area In the larger reactions the draining lymph nodes are swollen and tender Fever is usually present in infants at times reaching 104 or 105 F and remaining at that elevation for several days Extreme discomfort with chills aching and localized tenderness is common Also in such reactions small additional vesicles may occur about the periphery of the indurated area As a result of the irritation and itching infants will frequently scratch the vesicle and inoculate themselves elsewhere on the body at the site of open skin lesions or scratch marks As the reaction subsides the vesicle which is typically umbilicated becomes darker in color with a deeper central crater and gradually changes into a hard black crust which falls off in several weeks The remaining scar is bluish red at first and in time becomes a firm white area characteristically round and irregularly pocked

Failure to react in one of these manners is not an indication of immunity as is often incorrectly supposed but rather an evidence in almost all instances of an inactive virus vaccine In certain cases the lymph may have been washed off with soap and water or possibly methyl alcohol or some other improper antiseptic may have been used for preparation of the site of inoculation but it is probable that in only rare instances does the child fail to react when the virus is active and applied properly on a dry site Occasionally hypersensitivity reactions in the form of urticarial or maculopapular rashes appear seven to eleven days after vaccination When bullae occur the mucous membranes may be involved Such an erythema multiforme pluriorificialis may be quite serious

Care of Reaction Of primary importance in the care of the lesion resulting from the typical take is maintenance of dryness and a free flow of air about the vesicle For this reason shields should never be used In addition a relatively sterile surface may be maintained on the vesicle and on the entire area about the reaction by sponging them gently with alcohol and cotton at least twice daily being careful to leave the surface of the vesicle intact If a serous discharge occurs from the vesicle because of excessive tension or more commonly trauma alcohol and cotton should be used three to four times daily and a loose piece of gauze attached to the clothing over the vesicle or attached to the skin by adhesive tape placed well outside the indurated area If a discharge sufficient to cause crusting occurs so that the gauze becomes attached to the vesicle an antibiotic ointment may be applied to the vesicle at least twice daily following the usual cleansing with alcohol and a piece of gauze may be added as further protection for the clothing

Frequency of Vaccination Opinions vary as to the required frequency of revaccination but in general five to seven years may be considered a proper interval between vaccinations with the additional provision that vaccination be performed whenever epidemics of smallpox are impending

Complications and Sequelae The most dangerous complication of vaccination is that of pyogenic infection resulting from neglect dirt scratching and other skin infections Such infection is usually of staphylococcal origin with cellulitis but hemolytic streptococci may at times be responsible and septicemia erysipelas or scarlet fever may also be seen Such infections increase the size and severity of the reaction considerably and result finally in a large and disfiguring scar

Vaccinia gangrenosa or prolonged generalized vaccinia an almost invariably fatal but rather rare complication occurs as a slowly spreading gangrenous vaccinial involvement of the skin surrounding the take with serpiginous ulceration edema with gangrene and satellite takes which are incorporated into the slowly spreading swollen and gangrenous slough This is associated with extreme toxicity fever and incapacity of the skin to localize the infec

tion Many of these patients have agamma globulinemia

Hyperimmune human gamma globulin developed by Kempe and given parenterally in 10 ml amounts every one or two weeks for four to six weeks has been of curative value

The additional necrosis caused by pyogenic complications is an excellent medium for the growth of tetanus bacilli Tetanus occurs less frequently now than formerly but is still an important consideration where dirt and squalor prevail Under such conditions the use of tetanus toxoid for immunization should precede vaccination against smallpox The elimination of shields in the care of the usual "take" has also eliminated much of the danger of tetanus

Scratching may cause secondary vesicles at distant points particularly about the genitalia and face where severe scarring can occur A generalized vaccinia is seen at times in an infant with eczema or some other generalized skin disease when it has been exposed to another vaccinated member of the household If an eczematous child requires vaccination the hyperimmune gamma globulin should be injected in a single dose of 0 6 ml per kg of body weight for prevention of eczema vaccinatum The same dosage may be used for an eczematous contact or for treatment of a generalized vaccinia Umbilicated lesions may extend over most of the body with high fever and extreme toxicity In such cases lesions of the eye should be handled most carefully because of the danger of corneal perforation At times generalized urticaria roseola or purpura is seen when the reaction is at its height Occasionally viremia results in viral osteomyelitis with afebrile but extensive multiple bony necrosis and eventual slow healing Pyogenic osteomyelitis is rare

Postvaccinal encephalitis has rarely been reported in the United States but has been recorded more often in England and Europe It usually appears about ten days to two weeks after the height of the vaccination reaction although it may be seen earlier or later The severity of this complication appears to be entirely unrelated to the severity of the "take or to the batch of vaccine used The onset is generally abrupt with high fever disorientation and at times with coma or convulsions A stiff neck positive Kernig sign increase or absence of reflexes and positive Babinski sign are usually present Weakness and paralysis of the extraocular muscles are common as well as paralyses of the face pharynx and limbs As a rule the cells are increased

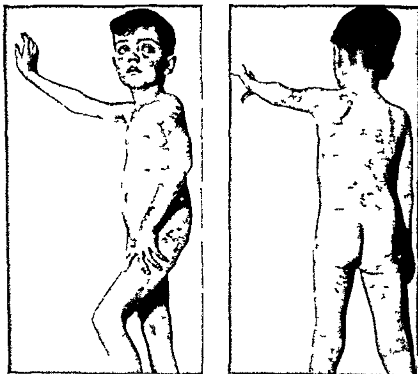


FIG 8 Hyperallergy expressed as roseola vaccinosa Note the marked area of the vaccination lesion on the arm

in the cerebrospinal fluid chiefly the lymphocytes although at first there may be an increase in polymorphonuclear cells The sugar and chloride of the cerebrospinal fluid ordinarily are not greatly altered but the protein is usually increased as is also the pressure The course of the disease is usually extremely stormy with either a rapid progression to death or an equally rapid improvement The case mortality of this complication ranges from 30 to 50 per cent and even though rapid improvement occurs residual mental retardation or spasticity may remain There is no specific therapy available other than lumbar punctures for relief of cerebrospinal fluid pressure and the proper orthopedic care of any paralyzed or spastic skeletal muscles It is of particular importance that this complication is almost never seen in infants less than one year of age and is practically unknown in the first months of life This constitutes a strong argument for early vaccination against smallpox

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Mumps

(Epidemic Parotitis)

Definition Mumps is an acute communicable disease caused by a virus It usually manifests itself by involvement of the salivary glands but frequently involves other tissues notably those of the testes and the central nervous system

History The clinical and epidemiological features of mumps were well described long before the etiology was known Advances in knowledge have been rapid since 1934 when Johnson and Goodpasture isolated the virus by inoculating saliva of patients into the parotid duct of monkeys Enders and associates developed a complement fixation test which made possible a definite diagnosis and was useful in epidemiological and immunological studies A notable advance was made by Habel who succeeded in growing the virus in chick embryos Levens and Enders then adapted the virus to the allantoic sac and demonstrated its hemagglutinating properties These developments facilitated studies on prophylaxis and immunization which have been carried on by Henle and associates Habel and others Infection of volunteers by Maris provided data on the frequency of subclinical infection and the period of communicability Kilham showed that the virus was pathogenic for suckling hamsters and mice

Etiology Mumps virus is of medium size with a diameter calculated by various observers to be between 90 and 135 mμ It is readily isolated from the saliva of patients with parotitis and from the cerebrospinal fluid of patients with meningo-encephalitis In monkeys it causes parotitis In suckling mice or hamsters it may cause fatal meningo encephalitis It grows readily but slowly in the yolk sac or amniotic *sac of chick embryos and can be adapted* to the allantoic sac After multiple chick embryo passages the virus may become less virulent for man Erythrocytes of chickens and humans are agglutinated by virus suspensions

Morbid Anatomy Observations of infected parotid tissue from humans are few In general the changes observed resemble those noted in infected monkeys Sero fibrinous exudate in the interstitial tissue vascular engorgement and lymphocytic infiltration of the tubules are noted Necrotic glandular cells and polymorphonuclear cells are found within the lumina Biopsy specimens from the testis show marked edema perivascular lymphocytic infiltration focal hemorrhages pronounced destruction of germinal epithelium and plugging of the tubules by epithelial debris fibrin and poly morphonuclear cells In most instances the lesions are focal and some areas escape

Pathological Physiology The serum amylase of most patients is elevated during the first few days of illness apparently because of the acute inflammatory process in the parotid glands rather than an accompanying pancreatitis

Incubation Period The incubation period is most frequently between seventeen and twenty one days Extremes of from eight to thirty five days have been reported

Communicability The virus has been repeatedly recovered from the saliva during the three days following onset and on one occasion as late as the sixth day after onset Experimental studies show that it may be present for several days before the onset of symptoms and may also be recovered from persons with inapparent infections It is presumed to enter the host by the oral or respiratory route through the medium of infected droplet or direct contact Spread to other tissues probably takes place by way of the blood stream The degree of communicability of mumps is relatively low Many persons reaching adult life are susceptible to infection

Age Incidence The disease is most frequent between the ages of five and fifteen All ages may be affected High attack rates have been noted in all age groups in isolated populations such as the inhabitants of Pacific islands

Immunity Immunity is generally of long duration Second or even more rarely third attacks have been reported but are exceedingly uncommon There is no convincing evidence that the patient with unilateral parotitis is any more likely to experience a second attack than one with a bilateral parotitis The development of immunity as a result of inapparent infection is a common occurrence

Clinical Manifestations *Parotitis* Before the appearance of parotid swelling there may be a prodrome of one or two days duration during which the patient experiences feverishness chilliness malaise anorexia and headache In mild cases this is not observed Swelling of one or both parotid glands then occurs In the latter event the two glands may be affected at the same time or in sequence The swelling is accompanied by variable amounts of pain about the angle of the jaw and by difficulty in moving the jaw

The swelling in the parotid region fills the area behind below and anterior to the angle of the jaw extending up to the zygomatic arch The lobe of the ear is pushed out and upward The affected glands feel firm and are moderately or extremely tender The orifice of Stenson s duct may appear reddened The temperature is usually between 100° and 103° F but may rise to higher levels By the second or third day the swelling has usually reached a maximum and begins to subside The time required for swelling to disappear completely is subject to considerable variation As a rule this occurs within a week but swelling may persist for considerably longer periods

Accompanying the parotitis or rather infrequently in the absence of obvious parotitis swelling of the submaxillary or sublingual glands may occur This is more readily determined by palpation than by inspection Edema of tissues surrounding affected glands is commonly observed and may involve much of the anterior surface of the neck and the area lying over the anterior surface of the manubrium sterni

Orchitis Orchitis is an infrequent manifestation of mumps before puberty but is common in adults The over all incidence has been estimated as approximately 20 per cent Considerable variation in incidence has been reported in different epidemics A small proportion of patients may have orchitis without evidence of parotitis

In general orchitis develops as the parotitis is beginning to subside Pain and swelling of the affected testis are noted and the temperature rises accompanied by chilliness and malaise The affected testis may enlarge to two or three times its normal size and is painful and exquisitely tender Epididymitis hydrocele and scrotal edema may be present Usually only one gonad is involved but both may be affected The swelling and constitutional symptoms progress for two or three days and then subside over a period of a week or more In certain instances fever drops precipitously rather than by lysis A considerable amount of atrophy as determined by palpation occurs in approximately one half of the patients but sterility seldom ensues This may be explained by the fact that even when there is extensive involvement of both testes the distribution of the inflammatory reaction is spotty and certain seminiferous tubules are spared Psychological rather than organic factors are presumably responsible for the occasional development of impotence following an attack of mumps orchitis

Meningo encephalitis Wide variations in the incidence of meningo encephalitis in different epidemics have been reported In certain series in which the cerebrospinal fluid has been examined routinely pleocy

tosis has been found in as many as one half and signs of meningo encephalitis in more than one fourth of the patients Though signs of central nervous system involvement commonly follow the development of parotitis they may be observed before or simultaneously with the parotid involvement Furthermore it is important to stress the fact that meningo encephalitis may occur in the absence of any salivary gland involvement

The temperature is usually markedly elevated in the presence of meningo encephalitis and the patient complains of severe headache photophobia neck stiffness nausea and vomiting Delirium may occur but in most instances the sensorium remains clear On physical examination the patient is often drowsy but can be roused the neck and back are stiff and Kernig s sign is present Lumbar puncture shows an increased cerebrospinal fluid pressure an increase in cell count and a slight increase in protein The cells are predominantly lymphocytes and the cell count though variable tends to be higher than in certain other neurotropic viral diseases The prognosis is favorable There is reason to believe that death when it occurs results from a chain of events initiated by the mumps infection rather than from a direct effect of the virus Convalescence may be slow but sequelae are uncommon

Other Manifestations Pancreatitis is suggested by the appearance of epigastric pain nausea and vomiting There may be tenderness on deep palpation and occasionally the pancreas is palpable Determination of the serum amylase is of no value in this situation however for elevated serum amylase values occur commonly in apparently uncomplicated mumps Oophoritis is probably not uncommon but the diagnosis is difficult to establish with certainty It should be considered when a patient complains of lower quadrant or low back pain and when a tender enlarged ovary is felt Other less common manifestations of mumps include mastitis in either sex involvement of lacrimal glands thyroiditis deafness seventh nerve paralysis and optic neuritis Myocarditis has also been described Polyneuritis and myelitis occur but can hardly be considered to be due to a specific effect of the mumps virus since they have been observed in a wide variety of infectious diseases

Diagnosis The clinical diagnosis in a patient with parotitis who has been exposed to mumps is seldom difficult Occasionally cervical lymphadenitis parotitis of bacterial etiology and salivary calculi must be considered The diagnosis may be more difficult when only submaxillary or sublingual glands are involved Meningo-encephalitis without accompanying parotitis must be differentiated from other neurotropic viral diseases in particular nonparalytic poliomyelitis A history of exposure to mumps is often an important clue When the issue is in doubt it can now be resolved by serological tests

Complement fixation agglutination inhibition and neutralization tests have been developed for the diagnosis of mumps In all tests two serum specimens should be tested for definitive diagnosis rests on the demonstration of a significant increase in antibody titer The first specimen should be taken as early as possible and the second between ten and twenty one days after onset

The total leukocyte count may be low normal or slightly elevated A considerable proportion of patients show a lymphocytosis Because this is not uniform the blood picture is not of great value in diagnosis

Prognosis The outlook is almost invariably favorable A fatal outcome is stated to occur less than once in a thousand cases

Treatment Patients should be kept at rest in bed Pain associated with parotitis can usually be relieved by salicylates supplemented if necessary by codeine Application of heat or cold may afford comfort In orchitis Demerol (0 05 to 0 1 gm) or morphine (0 01 to 0 015 gm) may be necessary The testes are more comfortable when supported Cortisone (0 1 to 0 3 mg per day) may relieve the pain and tenderness of mumps orchitis but does not prevent the manifestation of the infection The effect of cortisone on the sequel of testicular atrophy is not known

Convalescent serum and pooled gamma globulin have been recommended for alleviating the severity of the illness and preventing the development of orchitis Stilbestrol has been widely used in treating orchitis Evidence for the effectiveness of all these substances is conflicting There is limited but more convincing evidence that globulin prepared from serum which contains mumps antibody in high titer may reduce the incidence of orchitis

Prevention *Tests to Determine Susceptibility* Intradermal tests and measurement of serum antibodies have been used to determine susceptibility in exposed persons Both procedures may provide useful information but neither is infallible

Passive Immunization Gamma globulin

from normal serum or preferably from serum known to contain mumps antibody in high titer may prevent the development of mumps when given within a week of exposure Convalescent serum may also be effective but carries the risk of viral hepatitis even when irradiated Passive immunity is of short duration and the patient remains susceptible to infection later in life when complications are more likely to occur

Active Immunization Some reduction in the incidence of mumps has been shown among persons vaccinated with either inactivated virus preparations or with live virus attenuated by chick embryo passage The degree of protection obtained has fallen somewhat short of expectations

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Psittacosis

(*Ornithosis*)

Definition Psittacosis (ornithosis) is a specific infectious disease endemic among various members of the bird kingdom The infectious agent is transmissible to man in whom it usually induces an atypical form of pneumonia In a strict sense the term *psittacosis* designates the disease in birds of the order Psittaciformes (parrots parakeets and the like) and the disease communicated by them to man The discovery that birds belonging to other orders may be infected similarly and may transmit the infection to man led to the suggestion (Meyer) that all instances of the disease whether avian or human be included *under the broader term ornithosis*

History Psittacosis in man was a rarely recognized disease until 1929 The disease was described by Jurgensen 1876 and by Ritter 1880 who noted the association between it and the presence of ill birds Morange 1895 gave the disease its name The etiological agent was discovered by Bedson Western and Simpson 1930 who showed it to be filterable and present in infected tissues of parrots and human beings Levinthal and Coles as well as Lillie 1930 independently described elementary bodies" in infectious material Krumwiede McGrath and Oldenbusch 1930 demonstrated the susceptibility of mice to infection with psittacosis virus Rivers and Berry 1930 1932 induced psittacosis pneumonia in monkeys Coles 1940 showed that pigeons were infected with the virus and Meyer Eddie and Yanamura 1942 demonstrated that these birds could cause infections in man

Etiology The etiological agent is included among the viruses of the psittacosis lymphogranuloma group The agent of psittacosis one of the largest of known viruses has not been shown to be capable of multiplication in the absence of living cells Elementary bodies are readily demonstrable in infected tissues of birds mammals and human beings many investigators consider them to represent the virus

A number of different strains of the virus are recognized Infected birds represent the source of infection in the majority of human cases In man the disease appears to be more severe when acquired from members of the parrot family but pigeons have been responsible for numerous infections in human beings and some cases have been attributed to contact with infected canaries finches petrels or chickens Infected birds may or may not appear ill The virus is present in the nasal discharges and droppings of most infected birds and contaminates their feathers and cages It is relatively stable withstands prolonged drying and enters man via the upper respiratory tract Both sexes and persons of all ages are susceptible although children appear to be more resistant than adults The virus is present in the sputum of patients and direct transmission from man to man occurs although it is not common The disease usually occurs in a sporadic manner or affects small groups of persons exposed to a common avian source of infection

Morbid Anatomy Infection by viruses of the psittacosis lymphogranuloma group induces a variety of pathological alterations Among infected birds the lungs are seldom altered The chief abnormalities are seen in the liver and spleen which are enlarged and show areas of focal necrosis

In man the chief abnormalities are seen *in the lungs The pneumonic lesions are*

usually patchy and irregularly distributed They develop near the hilum and spread toward the pleura which is only rarely involved There is cellular infiltration of the alveolar walls and spaces lymphocytes and other mononuclear cells predominate

Pathological Physiology and Chemistry The leukocyte count is usually within normal limits although transient leukocytosis or leukopenia may occur and a relative monocytosis may develop Albuminuria is seldom marked and may be absent The erythrocyte sedimentation rate is increased Cyanosis is seldom a striking feature probably because the alveolar spaces in the pneumonic lesions are usually not completely filled with exudate

Symptoms The incubation period ranges from seven to fifteen days The symptoms vary widely as does the severity of the disease The source of the virus appears to be of some importance infections derived from birds of the parrot family are often more severe than those contracted from pigeons The onset may be abrupt or insidious The initial symptoms are malaise anorexia fever headache and backache Chills may occur The cough is usually nonproductive and may be severe and paroxysmal The temperature rises fairly rapidly is usually remittent and may remain elevated for two or three weeks after which it falls by lysis The pulse rate is usually slow in relation to the temperature The respiratory rate is often normal or only slightly increased Pleural pain is rarely present In severe cases a high temperature restlessness insomnia and delirium may develop headache cough and constipation with abdominal distention may be prominent features marked increase in both the pulse and respiratory rates may occur and indicates a poor prognosis

Pulmonary consolidation develops in the great majority of patients but may be difficult to detect by physical examination particularly during the first week of illness Usually it begins at the hilum and spreads outward Despite the absence or paucity of physical signs of consolidation roentgenograms of the chest usually show evidence of pneumonia early in the course of the disease The roentgenogram reveals hazy patchy irregularly distributed areas of increased density which are seldom lobar in distribution Pleural fluid rarely is evident and when present is small in amount Diarrhea epistaxis and even scattered macules resembling rose spots may occur Some patients produce large amounts of sputum which may be slightly blood streaked but is not rusty Extension and spread of the pneumonic process occurs frequently and migratory pneumonia has been observed Relapses occur occasionally Complications are not frequent but phlebitis may develop Convalescence is slow and after a severe attack may be prolonged

Diagnosis The development of symptoms and signs indicative of an atypical form of pneumonia in a person who has recently had contact with birds should suggest the possibility of psittacosis A normal respiratory rate a relatively slow pulse rate a normal leukocyte count the absence of classic physical signs of pneumonia and the presence of consolidation on the roentgenogram are characteristic but not pathognomonic Without the assistance of laboratory tests the disease rarely can be distinguished from atypical pneumonias of other etiology Mild cases may be confused with pulmonary tuberculosis or sporadic influenza Severe cases may resemble typhoid fever In appropriately equipped laboratories experienced personnel may be able to recover psittacosis virus from the sputum and thereby establish the diagnosis The complement fixation reaction with serum and psittacosis antigen is an important diagnostic aid

Prognosis The prognosis is influenced by the source of the virus the age of the patient the extent of pneumonia and prompt use of effective chemotherapy Infections derived from birds of the parrot family are most severe Infections contracted from other members of the bird kingdom appear to be less severe

Treatment Psittacosis in man could be eradicated if exposure to infected birds could be eliminated Birds belonging to the parrot family and pigeons appear to constitute the chief sources of human infections Patients with the disease may transmit it to those who care for them The virus is present in the sputum and may be disseminated by coughing

Psittacosis is one of the very few viral diseases for which specific treatment is available Chemotherapy with certain antimicrobial drugs is effective in the disease in man Sulfonamides are not of much value nor is streptomycin Penicillin in doses of 300 000 to 600 000 units per day may in some cases be helpful The tetracyclines are the drugs of choice and appear to be more effective than chloramphenicol Doses of 1 gm of a tetracycline drug by mouth every six to eight hours during the first two days and every twelve hours thereafter should be given for one week Sympto

matic and supportive therapeutic measures should also be used

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Lymphogranuloma Venereum

(*Lymphopathia Venerea Climatic Bubo*)

Definition Lymphogranuloma venereum is an infectious disease systemic in nature and varied in manifestations which produces specific involvement with acute and chronic inflammation of the lymph channels and nodes of the genitals and rectum The disease is transmitted by sexual contact Early manifestations include an evanescent genital lesion followed by subacute regional lymphadenitis progressing to suppuration and sinus formation General dissemination of the infective agent constitutional symptoms and rarely involvements of distant structures occur Later progressive inflammatory disease of the local lymphatics and surrounding tissues leads to lymphedema ulceration and disfigurement of the genitals and to proctitis perianal fistulas and rectal stricture

Etiology The causative agents of lymphogranuloma and psittacosis and of certain diseases of birds and animals are known as the psittacosis lymphogranuloma group and are tentatively classified intermediate between the viruses and rickettsiae Common characteristics of the psittacosis lymphogranuloma group include large particle size antigenic interrelationships and susceptibility to certain antimicrobial agents The lymphogranuloma microorganism is pathogenic for the chick embryo and produces meningo encephalitis on intracerebral inoculation into mice

Epidemiology Although lymphogranuloma venereum was long considered a disease of warm climates there is ample evidence of its world wide distribution As with other venereal diseases the prevalence of the infection is determined by the promiscuity of the population and is greatest in young adults Surveys based on intradermal reactions to killed lymphogranuloma agent suggest that inapparent infection and latent disease are frequent in promiscuous persons Existence of the carrier state has been shown by isolation of the agent from the genitals or rectum of asymptomatic persons of both sexes (Coutts) Accidental infections of laboratory personnel have been described

Pathogenesis After a variable incubation period of from three to twenty days an initial lesion (vesicular papular or ulcerative) may occur at the site of infection More commonly the first evidence of the disease is involvement of the inguinal lymph nodes beginning two weeks to three months after exposure the primary lesion having been unnoticed or absent

The inguinal adenitis unilateral or bilateral is a subacute diffuse process affecting the entire chain of lymph nodes and often the femoral group as well producing the sign of the groove" Characteristic of the inflammatory reaction is the formation of multiple small abscesses within the nodal parenchyma subsequently spreading to the surrounding pericapsular tissues and to the overlying skin The tissues become indurated matted and fused the skin reddened and brawny Pain and tenderness are variable Ultimately rupture of abscesses through the skin results in chronically draining sinuses

Systemic invasion by the lymphogranuloma agent may be manifested by fever



Fig 9 Lymphogranuloma venereum unilateral involvement five days after appearance of inguinal adenitis (Courtesy of Howard and Strauss New England Journal of Medicine)

arthralgias or arthritis various types of cutaneous eruptions and by ocular lesions in the form of conjunctivitis or iritis The nervous system may also be involved as evidenced by headache meningeal signs and abnormalities in the cellular and protein content of the cerebrospinal fluid The agent has been isolated both from locally involved sites and from blood and cerebrospinal fluid

In females the less frequent occurrence of early external manifestations is presumably related to the lymphatic drainage of the site of entry of the agent On this basis primary infection of the vulva or introitus results in inguinal involvement inoculation through mucous membranes of the upper vagina or cervix leads to inflammation of perirectal and pelvic lymphatics The latter type which in its early stages may simulate gonococcic disease has serious long term implications in the form of proctitis and rectal stricture

Late manifestations of lymphogranuloma venereum include disfiguring lesions of the external genitals (elephantiasis or in females esthiomene) and the anorectal syndrome In the former persistence of the infectious process in the skin subcutaneous tissues and lymphatics of the genitals produces brawny induration and slowly developing enlargement of affected soft tissues over periods of months or years Finally suppuration fistula formation and scarring lead to disfigurement and to functional impairment The anorectal syndrome is initiated early in the disease by proctitis with tenesmus and a bloody or purulent discharge Later chronic cicatrizing inflammation of the rectum and perirectal tissues leads to obstipation and to diminished caliber of the stools At the onset of rectal stricture edema is a contributing factor and at this stage the process is amenable to medical treatment The late fibrous stricture however may require colostomy In addition there may be involvement of the rectovaginal septum progressing to fistula formation Perianal fistulas also occur and because of lymphatic obstruction dilated perianal lymph channels (lymphorrhoids) resembling hemorrhoids develop It is to be emphasized that lymphogranuloma is the commonest cause of benign rectal stricture

Diagnosis Isolation and identification of the infective agent of lymphogranuloma are experimental rather than practical procedures Consequently the diagnosis must usually be based on clinical grounds combined with indirect laboratory evidence and the exclusion of other diseases Prior to the appearance of the lymphadenitis the primary lesion of lymphogranuloma may simulate herpes progenitalis Both early syphilis and chancroid mimic *early* lymphogranuloma Tuberculosis and lymphoma frequently require diagnostic consideration as may tularemia and plague under appropriate circumstances Clinical similarities as well as terminology cause confusion between lymphogranuloma venereum and granuloma inguinale a separate disease caused by the Donovan body *Late* anorectal lymphogranuloma must be differentiated principally from ulcerative colitis and cancer

To ensure the absence of early syphilis darkfield examinations of material expressed from genital lesions or aspirated from enlarged inguinal nodes should be performed as well as follow up serological observations It should be pointed out that false positive serological tests for syphilis occur in about 20 per cent of patients with lymphogranuloma The clinical manifestations of chancroid and lymphogranuloma may be indistinguishable

The *intradermal test* introduced by Frei now employs as antigen killed lymphogranuloma agent harvested from yolk sacs of chick embryos (Lygranum) Sensitivity develops in ten to thirty days after onset of the disease and persists for years in the absence of treatment Thus a positive reaction is indicative of either present or past infection The sensitivity of the test is high 90 per cent or more of patients with lymphogranuloma giving positive results Positive reactions are not induced by use of the test material itself but reactivation of latent lymphogranuloma has been described following this procedure Cross reactions with diseases due to other agents of this group may occur

The *complement fixation test* uses an antigen similar to the skin testing material As with the intradermal test a positive complement fixation reaction (except as noted subsequently) indicates present or previous infection In Heyman s study all of twenty seven patients with early lymphogranuloma proved by isolation of the agent had complemented fixation titers of 1 40 or more and most had titers of 1 160 or higher However more important than titer was the serological trend determined by study of acute phase and convalescent serums collected over periods of weeks frozen and tested simultaneously Cross reactions" may occur in infections due to other agents of the lymphogranuloma psittacosis group Ordinarily these do not constitute a prob-

lem because of differing clinical manifestations as well as because of the lower titer of most cross reacting serums In psittacosis however high titered complement fixation reactions with lymphogranuloma antigen may occur

Hyperglobulinemia Hyperglobulinemia with elevated total serum proteins and reversal of the albumin globulin ratio is common Although the increase in globulin may develop within a few days after the appearance of buboes several weeks or more may be required In addition administration of effective antimicrobial agents may prevent or reverse hyperglobulinemia

As chancroid may simulate lymphogranuloma with respect to both primary lesion and bubo diagnostic tests for both diseases should be carried out concurrently For chancroid smears and cultures employing appropriate techniques and an intradermal test using killed Ducrey bacilli as antigen have demonstrated value Inasmuch as the histopathology of each of these two venereal infections is distinctive and frequently diagnostic biopsy may prove helpful Biopsy is usually necessary for the diagnosis of either tuberculous lymphadenitis or lymphoma

Prognosis Early lymphogranuloma has a variable and unpredictable course Prompt diagnosis and adequate treatment to terminate infectiousness and to prevent late complications are important The longer the duration the slower and less complete is the therapeutic response The end stages of late lymphogranuloma fibrous strictures and scars are usually resistant to medical treatment

It has been suggested that there is an increased occurrence of genital and anal cancer in patients with symptomatic late lymphogranuloma In view of this possibility biopsy should be freely utilized in patients with known or suspected lymphogranuloma

Treatment Although penicillin has been demonstrated to be active against experimental lymphogranuloma infections it has not proved effective clinically in the dosages employed Both the sulfonamides and the tetracyclines are somewhat effective but the therapeutic response to either may be incomplete In the treatment of early lymphogranuloma with sulfonamides 3 or 4 gm should be administered daily for three to six weeks depending on clinical response For disease of long duration treatment may be initiated as above then the dosage decreased to 2 gm daily for a prolonged period (several months) With tetracycline compounds 500 mg four times daily is recommended The individual dose may be reduced later to 250 mg and continued three to six weeks for early infections and for more prolonged periods for late lymphogranuloma Combined sulfonamide and tetracycline therapy may prove more effective than either alone

Fluctuant buboes respond to repeated aspirations incision and drainage or the excision of involved structures is unnecessary and may be harmful With respect to rectal stricture digital dilatation should accompany administration of antimicrobial agents and combined treatment should be continued for several months if possible before resorting to surgical procedures Plastic operations on the genitals should likewise be deferred until the effects of antimicrobial therapy have been observed In spite of long standing disease surprising recovery of form and function may occur Conversely treatment may not be wholly effective even in early lymphogranuloma

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Foot and Mouth Disease

(Aphthous Fever)

Foot and mouth disease is a viral infection of animals chiefly cattle which occurs in man only with great rarity Infection when it does occur in man presumably results from direct contact with the virus either in the laboratory or from handling the tissues or body fluids of infected animals The disease in man is characterized by a short incubation period followed by

the appearance of a febrile illness with vesicular lesions of palms soles and the oropharyngeal mucosa Neurological in volvement has not been reported and the disease is self limited There is no treat ment of established value the tetracycline *drugs have yielded* inconclusive results in the treatment of animals Prevention of the disease in man has not been extensively studied for man generally has a high de gree of resistance to the infection An effec tive vaccine for use in cattle has been *developed*

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Lymphocytic Choriomeningitis

Definition Lymphocytic choriomeningitis is an acute disease of man characterized by a grippelike illness followed in certain in stances by an acute aseptic meningitis

Etiology The causative agent is a filter able virus of medium size pathogenic for guinea pigs hamsters and monkeys by various routes of inoculation and for rats and mice by the intracerebral route It pro duces inapparent infection with subsequent development of antibodies in dogs pigs and rabbits The virus belongs to the viscero *tropic group producing an interstitial type* of pneumonia areas of round cell infiltra tion particularly in the liver and chorio meningitis During infection a soluble anti *gen is produced to which complement* fixing antibodies develop in convalescence Neutralizing antibodies to the virus itself are distinct and do not appear until sev eral months after infection

Incidence The disease occurs sporadi cally Cases have been recognized in various parts of the United States the British Isles Europe and Asia It usually occurs in fall winter or spring

Epidemiology The virus is harbored by mice in which latent infection passes from one generation to the next Cases have been traced to direct or indirect contact with these rodents Dogs develop inapparent in fection with this virus and the ability of certain blood sucking insects to transmit the disease has been demonstrated so that other possible sources of human infection exist Among laboratory animals this infec tion is a frequent cause of difficulty be cause of its communicability and it has been contracted by a number of laboratory workers Transmission of infection from one human being to another has not been observed

Pathology Few proved fatal cases have been studied The principal findings have been interstitial bronchopneumonia and lymphocytic infiltration of the choroid *plexus and meninges in the acute phases* The meningeal inflammation subsides slowly and may occasionally be followed by thickening infiltration and scarring of the ventricular walls and subarachnoid space

Symptoms *The incubation period is short* Within a few days after exposure fever develops This is usually irregular and may be accompanied by chills and symptoms of "the grippe malaise headache general ized aches and pains and anorexia Pharyn gitis cough and signs of pneumonia may occur During this phase which lasts from a few days to two weeks there is leuko penia In some patients complete recovery ensues in others approximately fifteen to twenty days after exposure and often after a remission of a day or two the tempera ture again rises and evidence of meningitis appears headache drowsiness nausea vomiting nuchal rigidity Kernig s sign bradycardia and changes in the deep tendon reflexes During this phase the leukocyte count is usually normal and lumbar punc ture yields fluid under increased pressure with elevated protein normal concentration *of glucose and from 50 to 2500 cells per* cu mm almost all lymphocytes The meningeal phase lasts about a week with gradual subsidence of fever and symptoms *but considerably slower disappearance* of the changes in the cerebrospinal fluid Cases exhibiting only the systemic symp toms of the prodromal phase have been diagnosed rarely but probably occur as often as cases of meningitis The majority of proved cases have had the syndrome of aseptic meningitis (see section on Non purulent Meningitis) Several patients have been observed in whom the stage of inva sion of the central nervous system was characterized by encephalomyelitic symp toms with both motor and sensory disturb *ances Rare fatal cases with encephalitis or* with pharyngitis pneumonitis high fever prostration and leukopenia which grad ually changed to a leukocytosis have been described

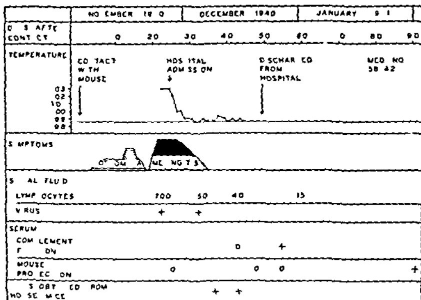


FIG 10 Course and laboratory findings in a patient with proved lymphocytic choriomeningitis probably acquired from handling a recently trapped mouse since the virus of this disease was subsequently obtained from mice trapped in the home (Reprinted from Medicine Vol 21 with permission of the publishers Williams and Wilkins)

Diagnosis The syndrome of "acute aseptic meningitis" originally described by Wallgren is relatively common Only a few instances are actually due to the virus of lymphocytic choriomeningitis The latter should be considered when there has been an exposure to mice other animals capable of harboring the virus or blood sucking insects and in patients who have had a prodromal illness of several days duration with a latent period before the development of meningitis The diagnosis is proved on isolation of the virus by inoculation of guinea pigs with blood taken during the prodromal phase or with cerebrospinal fluid obtained during the meningeal phase Intracerebral inoculation of white mice with infectious material gives rise to characteristic convulsions and death in six to ten days Serologic diagnosis depends upon demonstration of the development of complement fixing antibodies for the soluble antigen (four to six weeks after onset) and of neutralizing antibodies for the virus which appear later (two to three months after onset)

A common cause of acute aseptic meningitis is mumps It occurs in infectious mononucleosis and in infections due to many viruses capable of invading the central nervous system In any case of a lymphocytic reaction in the cerebrospinal fluid the possibility of parameningeal infection brain abscess torulosis tuberculosis leptospirosis and syphilis should be excluded

Prognosis Most patients recover completely Death due to overwhelming infection and sequelae due to fibrosis and scarring of the choroid plexus or meninges have been observed occasionally

Treatment Treatment is purely symptomatic

Prevention Control of rodents and vermin in the home and in places where laboratory animals are kept should reduce the incidence of the disease Persons trapping mice should handle animals and traps with care

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Rabies

(*Hydrophobia Lyssa*)

Definition Rabies is an acute infectious disease of the central nervous system to which all warm blooded animals and man are susceptible The virus frequently present in the saliva of an infected host is usually transmitted by bites or licks The disease characterized by a profound dysfunction of the central nervous system ends almost invariably in death

History Rabies was probably the disease to which Homer referred in the Iliad when he wrote κυ α λυσση ηρα Democritus and Aristotle recognized it as a disease of animals and Celsus described its transmissibility to man Rabies as a disease of wild animals had been known in Europe as early as the thirteenth century and in the eighteenth century epizootics among domestic animals were recorded in urban centers It was first reported in the Americas in 1709 by Fray José Gil Ramirez in Mexico and was described in the Virginia Colony in 1753 Since that time its presence has been evident throughout the North and South American continents

The transmission of rabies from the saliva of a rabid dog to a normal dog was first recounted by Zinke in 1809 and in 1879 Galtier described the susceptibility of rabbits to rabies and their use for diagnostic purposes The modern concept of the disease was developed by Pasteur and his associates (1881) They not only identified the causative agent but also were able to modify its pathogenicity by serial intracerebral passages in laboratory animals (1884)

Etiology, Host Range and Experimental Infection Virus recovered in nature the so called *street virus* is characterized by extremely variable usually long incubation periods and by its ability to invade salivary glands as well as central nervous tissue The term *fixed virus* is used for strains of rabies which have been adapted to laboratory animals by means of serial intracerebral passages Fixed virus is characterized by a short incubation period (usually four to six days) and by its apparent inability to multiply in salivary glands Prolonged cultivation of some strains of rabies virus in the developing chick embryo has resulted in modification to the point of complete loss of pathogenicity for animals injected extraneurally

In discussing the properties of the virus both the type of virus and the source of infected material have to be considered In general it may be said that the virus having a diameter of 100 to 150 mμ can be filtered through bacteria retaining porcelain filters It is filterable but not readily through Seitz EK filter pads Rabies virus is speedily inactivated by sunlight ultra violet irradiation formalin bichloride of mercury and strong acids It is relatively resistant to ether and chloroform and quite resistant to phenol In aqueous solution its thermal death point is reached at 56° C after an exposure of one hour It survives desiccation from the frozen state and may be best preserved in dry form

The host range of rabies is one of the widest in the disease spectrum All mammals including bats are susceptible The virus is also pathogenic for birds but to a lesser degree than for mammals The disease is not transmissible by insects or arthropods The virus cannot invade the body through intact skin and is apparently harmless when ingested However infection through unabraded mucosa seems possible

Rabbits guinea pigs Swiss albino mice and hamsters are most commonly employed for experimental infection Hamsters are remarkably susceptible to intramuscular injection with street virus but intracerebral injection of albino mice is usually employed for diagnostic purposes

Epidemiology and Epizootiology Johnson distinguishes two epidemiological patterns of the disease the natural sylvatic type maintained in wildlife and the urban type which occurs in domestic dogs The sylvatic type is present in enzootic form in many areas of the world in such wild animals as wolves (Arctic regions of Canada Eastern Europe Turkey Iran) mongooses (South Africa the Caribbean) bats (Central and South America and the United States) foxes coyotes skunks (United States) In the urban type a number of domestic animals including cows and cats may become involved but the propagation of the virus in dogs is solely responsible for the epizootics after the elimination of canine rabies there is no evidence that rabies persists in urban areas

Epizootics of rabies can occur in any climate during any season of the year Wars and mass movements of men and animals favor the geographical spread of the disease Man becomes an accidental host upon exposure to the infected saliva of the biting animal and although wild animals are often sources of human rabies dogs are mostly responsible for human infection The attack rate in man following exposure depends to a certain extent on the location and severity of the inflicted wounds Head and neck bites lead to a higher incidence of infection than bites on other parts of the body Although the bites of rabid wolves

are apparently very dangerous an attack rate of 47 per cent was recently observed in 32 persons bitten by the same animal

Morbid Anatomy At autopsy the brain is friable edematous and congested the convolutions are broad and flattened Marked vascular congestion of the white and gray matter may extend to the medulla and the spinal cord Virus infected salivary glands are usually soft and swollen On microscopic examination of the central nervous system the nonspecific findings consist of hyperemia perivascular and perineuronal infiltration with mononuclear cells and marked neuronal degeneration Mononuclear cell infiltration of periacinal interstitial tissue accompanied by degeneration of acinar cells may be observed in the parotid sublingual and submaxillary salivary glands

If proper staining technique is applied intracytoplasmic inclusion bodies can be demonstrated in the neurons of the majority of rabies cases These so called Negri bodies are pathognomonic for rabies encephalitis In their absence the lesions cannot be distinguished from those observed in other viral encephalitides

Incubation The incubation period varies from ten days to over twelve months As minor and seemingly insignificant contacts with rabies virus in the saliva of an animal not obviously sick at the time of exposure are sometimes forgotten claims of extended incubation periods (one to two years) have to be critically evaluated In dogs signs of rabies may appear after an incubation period of ten days to several months In one instance rabies developed in a dog eight and one half months after artificial exposure by intramuscular inoculation with street virus

The length of the incubation period is related to the amount of virus introduced at the time of exposure and to the severity of the laceration The site of the original exposure does not seem to affect the duration of the incubation period

Clinical Manifestations *Dogs* In dogs the prodromal phase of the disease consists of fever failure to eat hyperesthesia and very frequently change in the tone of the bark However these signs are often so slight that only a trained observer may note them Altered disposition of the animal is also characteristic The prodromal period may last from a few hours to several days and gives way to the excitation phase in which the animal grows unnaturally restless and agitated General tremor due to stimulation of the muscular system is frequent In the furious type of the disease agitation intensifies as the illness progresses The animal erratic and aggressive growls and barks constantly It will grab viciously at any object or animal encountered At this stage an unrestrained animal sometimes leaves home and travels great distances inflicting damage on other animals and humans along the way Convulsive seizures are often observed and the animal may become completely paralyzed In many cases however the excitation phase predominates until the time of death

In the paralytic type of rabies the excitation phase may be slight or totally absent and the disease is characterized only by the paralytic syndrome Paralysis of the lower jaw accompanied by excessive salivation appears as an early symptom and the animal acts as though choking on a foreign body Paralysis of the muscles of phonation may lead to loss of the bark As the disease progresses paralysis of the posterior extremities sets in followed by general paralysis and death The time from the onset of the disease to the death of the animal ranges from one to eleven days On the other hand dogs may die suddenly without noticeable signs of illness

Man In man the prodromal phase is marked by fever malaise nausea and sore throat Abnormal sensations around the site of infection such as intermittent pain tingling or burning are of diagnostic significance Extreme stimulation of the general sensory system is manifested by hyperesthesia of the skin to temperature changes and to drafts and by acute sensitiveness to sound and light Increased muscular tonus prompt gag and corneal reflexes dilation of pupils and increased salivation may be present

As the disease progresses spasmodic contractions of the muscles of the mouth pharynx and larynx on drinking—and later at the mere sight of fluid—are observed in the majority of cases This dysfunction of deglutition lent the disease its common name *hydrophobia* or fear of water Spasms of respiratory muscles and convulsive seizures leading to opisthotonos may occur The pulse is very rapid Periods of irrational and often maniacal behavior are interspersed with those of alertness and responsiveness Paralysis of the muscles of phonation may lead to hoarseness or loss of voice

The excitation phase may remain predominant until the time of death However in many cases it gives way shortly before

Indications for Specific Post Exposure Treatment*

NATURE OF EXPOSURE	CONDITION OF ANIMAL At time of exposure	CONDITION OF ANIMAL During observation period of 10 days	RECOMMENDED TREATMENT
I No lesions Indirect contact only	Rabid	—	None†
II Licks			
1 Unabraded skin	Rabid	—	None†
2 Abraded skin scratches and abraded or unabraded mucosa	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately Stop treatment if animal is normal on fifth day after exposure
	(d) Rabid escaped killed or unknown	—	Start vaccine immediately
III Bites			
1 Simple exposure	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately Stop treatment if animal is normal on fifth day after exposure‡
	(d) Rabid escaped killed or unknown or any bite by wolf jackal fox bat or other wild animal	—	Start vaccine immediately
2 Severe exposure (multiple or face head or neck bites)	(a) Healthy	Healthy	Hyperimmune serum immediately No vaccine as long as animal remains normal
	(b) Healthy	Clinical signs of rabies or proved rabid	As in III 2 (a) but start vaccine at first sign of rabies
	(c) Signs suggestive of rabies	Healthy	Hyperimmune serum immediately followed by vaccine Vaccine may be stopped if animal is normal on fifth day after exposure
	(d) Rabid escaped killed or unknown Any bite by wild animal or bat	—	Hyperimmune serum immediately followed by vaccine

Hyperimmune serum to be effective must be given within 72 hours of exposure
These indications apply equally well whether or not the biting animal has been previously vaccinated
* Prepared by Expert Committee on Rabies of World Health Organization
† Start vaccine immediately in young children and patients where a reliable history cannot be obtained
‡ Alternative treatment would be to give hyperimmune serum and not start vaccine as long as animal remained normal

death to cessation of muscle spasms hyporeflexia or areflexia and to general paralysis of the flaccid type

In some cases particularly those in Trinidad resulting from vampire bat infection the excitation phase is almost totally absent and the disease is characterized by ascending paralysis without hydrophobia Without an adequate history of exposure this type is indistinguishable from other viral encephalitides and the diagnosis may be overlooked

Diagnosis Profound dysfunction of the central nervous system accompanied by impairment in deglutition following a history of exposure to a bite or lick of an animal facilitates the clinical diagnosis Isolation of virus from saliva obtained in the course of the disease and from brain tissue obtained at autopsy followed by proper identification of the agent by means of neutralization test will confirm the diagnosis Syrian hamsters rabbits guinea pigs and mice are used for diagnostic purposes The presence

of Negri bodies is pathognomonic but their absence does not exclude the diagnosis of rabies encephalitis since isolation of the virus may still be accomplished

Prognosis Although inapparent infection with street virus may be induced artificially in laboratory animals and although animals have recovered completely after exhibiting signs of the disease *there is no proved instance of the recovery of man from rabies*

Treatment Prevention A treatment for rabies does not exist in the strict sense of the word for there are no therapeutic measures available which would save the life of a person exhibiting symptoms of the disease *A protective type of treatment* can be used following exposure to the virus and prior to the development of the disease Particularly in a rabies endemic area and adjacent territory this protective treatment has to be based on the assumption that every animal inflicting a wound on a human may be rabid until proved otherwise by clinical observation or by failure to discover the virus in its tissues after death

Local Treatment of Wounds All bite wounds including skin abrasions exposed to licks of animals should be treated *immediately* by thorough cleansing with soap or detergent solutions This does not preclude the use of strong mineral acids such as nitric acid which may be particularly useful in the treatment of deep puncture wounds where other methods of cleansing are not very effective In laboratory animals a cationic detergent Zephiran chloride applied in a 1 per cent solution to wounds artificially contaminated with the virus has been found to be effective in preventing rabies In another series infiltration of the wound with antirabies serum together with thorough cleansing and application of nitric acid where the site permitted gave excellent results

The local or parenteral application of an antimicrobial drug is of no value as a prophylactic measure except in combating concomitant bacterial infections

Indications for Specific Treatment These are summarized in a table prepared by the Expert Committee on Rabies of the World Health Organization Emphasis is placed on the condition of the biting animal at the time of the exposure and during the ensuing ten days It is assumed that the saliva of an animal which is not obviously ill at the time of exposure may be infectious during a maximum period of five days preceding the appearance of clinical signs of disease

Passive immunization against rabies by the administration of hyperimmune anti serum is introduced as a standard procedure in view of the overwhelming experimental evidence obtained in favor of such treatment Because of the existence of various vaccine preparations no emphasis is placed on the use of any special type of vaccine provided it meets the standard potency requirement

Administration of antirabies vaccine may give rise to local allergic reactions and to those of a general neuroparalytic nature The latter are caused by the presence of nervous tissue in the vaccine and occur most frequently during a repeated course of protective treatment No vaccine preparation is at present available which is free from the paralysis producing factor and therefore the administration of vaccine should be interrupted if even slight signs of dysfunction of the central or peripheral nervous system are observed By the same token antirabies vaccine treatment should not be given unless specifically indicated (see table)

Control Measures The majority of human exposures can be prevented by the use of control methods which will rid an area of enzootics or epizootics of rabies

The following measures should be applied in an efficiently organized rabies control program conducted by public health authorities control of the canine population (registration restraint elimination of stray dogs) reduction in number of susceptible dogs by mass vaccination reduction in number of wildlife species which are a reservoir of the virus and continuous educational campaigns for the general public

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Coxsackie and ECHO Viral Infections

Since the discovery of Coxsackie viruses by Dalldorf and Sickles in 1948 new viral techniques utilizing suckling mice and tissue cultures have led to the demonstration not only of *twenty four distinct* Coxsackie serotypes but also of numerous other newly recognized viruses grouped together under family names such as ECHO viruses (twenty serotypes) and *adenoviruses (eighteen serotypes)* Other apparently new virus strains remain to be classified Many if not most of the presently classified viral serotypes *are prevalent* infections of man everywhere The pathogenic activities of many of the sixty two distinct serotypes are unknown however and some of the others are expressed as subclinical or very mild easily overlooked illnesses Because of their very high prevalence multiple infections are frequent and spurious etiological associations are not uncommon Some representatives of each group however have been definitely established as causes of clearly evident common ill nesses The illnesses caused by adenoviruses are discussed elsewhere (see p 7)

Coxsackie Viruses At the present writing the twenty four distinct Coxsackie virus serotypes are separated arbitrarily into groups A and B on the

Illness Caused by Coxsackie and ECHO Viruses (Enteroviruses)

DISEASE	ETIOLOGY (Viral serotypes incriminated) (1958)	PREVALENCE AND CHARACTERISTIC OCCURRENCE (All are chiefly diseases)	DIFFERENTIAL DIAGNOSIS	COMMENTS
Herpangina (*vesicular pharyngitis*)	Coxsackie group A 2 4 5 6 8 10 (probably 3)	Most commonly as frequent sporadic illnesses in young children Recognized mostly however in localized community and institutional epidemics	Herpetic stomatitis with ulcerative pharyngitis Summer fevers due to Coxsackie B ECHO and adeno viruses	Often called summer grippe or summer pharyngitis when characteristic pharyngeal lesions not observed
Epidemic Pleurodynia (Bornholm disease)	Coxsackie group B 1 2 3 4 5	Mostly epidemic Less common than group A infections but reccognized with greater frequency	Acute medical and surgical emergencies — coronary occlusion acute appendicitis cholocystitis	Most common in children but in isolated rural communities all age groups may be infected Sequelae orchitis aseptic meningitis
Aseptic Meningitis (nonbacterial meningitis)	Coxsackie A 7 9 Coxsackie B 1 2 3 4 5 ECHO 4 6 9 (14) (Polioviruses 1 2 3 also)	Enteroviruses are major cause of the aseptic meningitis syndrome in young children	Aseptic meningitis due to mumps herpes lymphocytic choriomeningitis arthropod encephalitis poliomyelitis viruses leptospirosis	Etiological diagnosis depends entirely on identification of viral cause
Epidemic Exanthemata (Boston exanthem) (meningo-encephalitis with rash)	ECHO 9 ECHO 16	ECHO 9—extensive epidemics of meningitis with rash reported throughout Europe in 1956 ECHO 16—localized epidemics of Boston exanthem in U S A	Common childhood exanthemata	ECHO 9 also has the attributes of a Coxsackie group A virus
Myocarditis Neonatorum (acute aseptic myocarditis)	Coxsackie B 3 and 4	Proved cases recognized chiefly in newborn nurseries and clinics Intrauterine infection reported in one well studied case	Idiopathic myocarditis and sequelae of other viral infections	Frequently fatal outcome Associated with community epidemics of pleurodynia and aseptic meningitis

basis of their differing behavior in mice The nineteen group A viruses produce generalized myopathy in striated muscle and no other lesions in suckling mice The group B viruses on the other hand produce in suckling mice fewer and less severe muscle lesions but produce in addition pancreatitis encephalitis hepatitis and myocarditis The group B viruses also produce pancreatitis (lysis of acinar cells) in adult mice whereas group A viruses appear unable to grow and produce lesions in older mice Recently two viruses A 7 and A 14 have been shown to produce neuronal lesions in monkeys and the former has been incriminated by Russian workers as a possible cause of paralytic poliomyelitis in humans While most group A viruses will not grow in monkey kidney cultures which are commonly used for demonstrating and propagating ECHO and polioviruses A 7 A 9 and the five group B viruses do grow in this tissue and produce somewhat similar cytopathogenic effects

Besides their prevalence during the summer months Coxsackie viruses resemble the poliomyelitis viruses in other respects They are very small and they occur in comparatively large amounts in oral secretions and in stools They are resistant to antimicrobial drugs commonly used germicides and natural conditions unfavorable to the survival of most other viruses undoubtedly this accounts to some extent for their widespread occurrence in man and in his environment particularly in sewage and on flies Several strains have been found in mosquitoes

ECHO Viruses During a meeting of the WHO Expert Committee on Poliomyelitis (Geneva July 15 to 20 1957) it was observed that Coxsackie and ECHO viruses share certain properties with the polioviruses such as size seasonal incidence and epidemiological patterns and consideration was given to the concept that all viruses of similar size in the Coxsackie ECHO and poliovirus groups may be members of a single group of human enteroviruses Thus these three groups of viruses may soon be officially regarded as separate genetic representatives of a single family of human viruses

Representatives of the ECHO (enteric cytopathogenic human orphans) group of viruses share the following properties (Committee on the ECHO Viruses National Foundation for Infantile Paralysis)

1 They are cytopathogenic for monkey and human cells in culture
2 They are not neutralized by pools of the three types of poliomyelitis antiserum
3 They are not neutralized by antiserums for Coxsackie viruses that are known to be cytopathogenic in tissue culture and they fail to produce disease in infant mice

It is interesting that ECHO 9 and 10 have been found since this report to produce Coxsackie like lesions in suckling mice Indeed ECHO 9 was originally reported by several workers initially as an unidentified Coxsackie Group A virus However the virus was first classified as an ECHO 9 and will be so designated here

Illnesses Due to Coxsackie and ECHO Viruses The illnesses caused by Coxsackie and ECHO viruses occur chiefly but not entirely in young children during the warm months of the year The illnesses are quite heterogeneous in their clinical manifestations Perhaps the most common manifestation of infection in the very young with both groups of viruses is an undifferentiated febrile respiratory illness usually described nondescriptively as fever of unknown origin or summer grippe However certain serotypes are well established as causes of specific nosological clinical entities such as *herpangina* and *epidemic pleurodynia* and in addition such clinical syndromes as *aseptic meningitis* and *acute aseptic myocarditis* of the newborn The most recent entity in which ECHO viruses have been incriminated is an epidemic exanthema occurring in outbreaks with and without associated aseptic meningitis There is also evidence that certain ECHO and Coxsackie viral infections may be responsible for summer diarrheas in infants however their role in this symptom complex is still to be defined

HERPANGINA

(Vesicular Pharyngitis Aphthous Pharyngitis)

Definition Herpangina is a mild specific disease characterized by fever lassitude and small papular vesicular and ulcerative lesions in the soft palate and the faucial areas Although it is one of the most frequent summer illnesses of early childhood the specific nature of the illness in individual cases is often missed by the clinician it is somewhat more often recognized when it occurs in epidemic form in newly established residential areas or in summer camps for children

History The disease was first recognized as a specific entity by Zahorsky in 1920 He suggested the name herpangina" in a report of 80 cases in 1924 Reports of outbreaks of a similar illness in a summer camp and nursery school appeared in 1939 and 1941 The illness was not reported again until 1950 when certain group A Coxsackie viruses were suggested as etiological agents Since 1950 the disease has been recognized with increasing frequency and viral studies have repeatedly confirmed certain group A viruses as etiological agents Reports of the same agents found in association with similar illnesses in other countries leave little doubt that herpangina is a common occurrence in all parts of the world and that it is one of the most common manifestations of group A Coxsackie viruses

Etiology and Pathology Six strains of group A viruses have repeatedly been found causing herpangina (see table) The virus types found in herpangina while immunologically distinct from each other produce after brief incubation identical generalized destruction of the skeletal muscles of suckling mice and hamsters—followed promptly by death No other lesions are observed Mice over two weeks of age are completely resistant

The pathology of herpangina in man is obscure The illness does not result in death consequently postmortem tissues are not available Biopsies of muscle tissue from a typical case revealed neither pathological changes nor the presence of virus

Epidemiology The disease has been found during the summer months in nearly every community in which an effort to find cases has been made Most illnesses occur in early childhood As many as 10 per cent of children randomly selected from urban pediatric clinics have been found

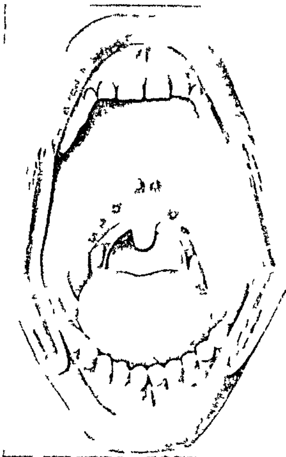


Fig 11 Herpangina lesions

harboring herpangina strains of virus during July August and September

In a household or a neighborhood herpangina viruses rapidly infect nearly all intimate susceptible contacts including an occasional parent However even when under constant surveillance only about 30 per cent of those persons infected manifest typical faucial lesions Nevertheless a variable number of the infected family contacts will present a similar picture of mild febrile illness without the typical throat lesions As in poliomyelitis and many other viral infections a large proportion of the infections are not attended by any clinical manifestations

Although immunity to the infecting strain appears permanent the frequent presence of other strains in the community provides ample opportunity for a repetition of the typical illness within the same or a subsequent summer Herpangina has been observed twice within one year in several children each subsequent episode being caused by a strain different from that found during the initial illness Most urban adults possess neutralizing antibodies against herpangina viruses the number of types neutralized increasing with age Unlike age differences in sex and race have not been associated with observable differences in attack rates

Clinical Manifestations In a typical case the disease begins with a sharp elevation of temperature (102° to 105 F) In the very young vomiting is common and convulsions may occur The patient complains of headache and frequently of pain and tenderness in the neck abdomen and extremities Infants often salivate excessively and refuse food Older children usually complain only mildly of a sore throat During the first twenty four to forty eight hours the fever reaches its peak and only minute petechiae or papules may be observed on the soft palate and tonsillar pillars twelve to twenty four hours later two to six superficial ulcers with grayish bases surrounded by red areolae are observed at these sites (Fig 11) The ulcerations heal within one to five days Fever seldom lasts longer than three days and by the fourth day the patient is usually asymptomatic There are no complications and a good immune response is produced Hematological and cerebrospinal fluid studies have revealed no characteristic abnormalities

Diagnosis In a typical case a clinical diagnosis of herpangina is not difficult if a careful inspection of the pharynx is made particularly when as frequently occurs there are similar cases in the household or the immediate neighborhood Herpetic stomatitis occurs at all seasons of the year and is characterized by larger more persistent and more painful ulcers in the anterior part of the mouth lesions seldom occur exclusively in the pharynx When laboratory facilities are available and suitable viral procedures can be carried out differential diagnosis can be made by recovering either Coxsackie or herpes viruses from lesions or by demonstrating a specific rise in antibody titer Unfortunately few laboratories are at present in a position to perform such studies Recurrent aphthae and Bednar s aphthae seldom occur in the pharynx and are not usually associated with constitutional symptoms

Relation to Poliomyelitis The distribution and spread of herpangina parallels that of poliomyelitis and simultaneous infection with agents of both diseases is common In a mixed epidemic a majority of persons infected with either or both of these agents can be expected not to show pathognomonic signs of specific illness and when they do show signs of illness characteristic of one agent this fact does not exclude infection

with the other. Thus a clinical separation of herpangina without pharyngeal lesions from nonparalytic or "abortive" poliomyelitis without cerebrospinal fluid abnormalities may on many occasions be extremely difficult if not impossible. Even laboratory efforts to unscramble mixed outbreaks are liable to encounter insurmountable difficulties unless accompanied by exhaustive epidemiological studies.

Prognosis. The disease tends to run a mild course; it may occasionally seem more severe in an adult. No complications or deaths have been reported. The ability of the physician to recognize this illness and give a hopeful prognosis is much appreciated by parents worried about poliomyelitis, often occurring at the same time in the community.

Treatment. None of the antimicrobial drugs appears to influence the severity or the duration of herpangina. Symptomatic treatment is often efficacious and should be used when indicated.

EPIDEMIC PLEURODYNIA

(*Bornholm Disease, Epidemic Myalgia, Devil's Grip*)

Definition. *Epidemic pleurodynia is an acute specific viral disease characterized by sudden onset of severe paroxysmal pain in the region of the attachment of the diaphragm which is aggravated by respiration and accompanied by intermittent fever, headache, anorexia and malaise. Because they are uncommon except during epidemics, the specific nature of such alarming symptoms occurring abruptly in previously healthy persons often is not recognized.*

History. The disease was first described by Daae and Homann in Norway in 1872. Although Finsen observed the disease in Iceland as early as 1856, he did not publish these observations until 1874. In 1888 Dabney described the first outbreak in the United States. Following extensive observations of this disease on the Island of Bornholm, Sylvest in 1933 published a monograph reviewing all previous reports, thus stimulating much interest in this disease. Numerous reports of outbreaks in England and the United States followed. Although viral etiology was postulated by many observers, all efforts to demonstrate such an agent failed until 1949, when a Coxsackie virus (type B 1) was found in relation to sporadic cases in Connecticut.

Etiology and Pathology. All group B Coxsackie viruses have been confirmed as etiological agents of epidemic pleurodynia (see table). The specific pathology of this disease in man is unknown, since a post mortem examination has never been reported. The occurrence of high fever and the demonstration of Coxsackie B type viruses in throat secretions and stools suggest a generalized infection.

Epidemiology. Most reports of epidemic pleurodynia have come from Europe and the United States, where outbreaks have been described over wide geographical areas. Strictly a summer and early autumn disease, the illness occurs in all age groups but is most common in children and young adults. Long-lasting immunity against the infecting strain of virus results. Although endemic areas have occasionally been described, pleurodynia is not generally prevalent each summer, and most reports deal with sharp outbreaks confined to geographically limited areas.

Most evidence suggests person-to-person spread, and multiple cases frequently occur in a household. The incubation period appears to be three to five days. Many apparently susceptible household contacts may escape infection. Unlike group A infections, infection with a group B virus is nearly always associated with a clinically apparent illness, not always, however, in the form of typical pleurodynia.

Clinical Manifestations. The disease begins with sudden onset of pain in either the abdomen or the chest. Although fever invariably follows in all cases, it is pain in the epigastrium, often shifting to the lower part of the anterior thorax on either side, which is the most characteristic manifestation of epidemic pleurodynia. The pain is *frequently so extreme that the patient* seems on the verge of collapse. He is observed *breathing rapidly and shallowly,* leaning forward and to one side, splinting *his chest by holding one arm tightly against* it. It is obvious that both movement and respirations aggravate the pains. The physi*cian faced with such a spectacle is moved to* administer analgesics or opiates promptly unless a surgical emergency is suggested. In either case, arrangements for hospitalization may be made—then cancelled within the hour because the patient rather suddenly feels well—all negotiations to be reopened a short time later by a recurrence of severe pain. After several such attacks the patient becomes extremely apprehensive of future exacerbations and is usually content to remain in bed for several days. The patient often has difficulty describing his pain accurately, localizing it over the area of the epigastrium and in the region of the attachment of the diaphragm. Very often the patient expresses his difficulty by saying "I can't breathe" or "It hurts to breathe," indicating a feeling of constriction in the chest—a feeling which undoubtedly led to the early American designation "Devil's grip" for this disease. The pain is described

as a dull ache 'like a toothache occasionally as a stabbing pain Children are usually *restless with knees drawn up their* sobbing or crying jerkily interrupted by painful stitches Convulsions are common in infants during bouts of high fever Moderate tenderness in the affected area is often accompanied by hyperesthesias localized muscle swellings and altered reflexes the latter most often in the abdominal areas

Fever a constant finding during the *initial attacks may occasionally* exceed 104° F but usually will fluctuate from 101 to 103 F The fever is intermittent recurring usually during exacerbations of pain Other prominent symptoms are headache sore throat and malaise Nausea and vomiting occur during the early stage of illness in young children however the severe pain tends to suppress excessive vomiting *Although pleural rubs are* occasionally reported there appears to be no evidence of lung involvement and coughing is conspicuously absent Hematological findings are usually within normal limits *Relapses may occur a few days after apparent recovery* and may continue to occur over a period as long as a month

Complications Orchitis lasting three to seven *days appears to be the complication* most frequently reported occurring in nearly all large outbreaks Fibrinous pleuritis is irregularly reported but it is not uncommon Aseptic meningitis has been reported as an infrequent complication perhaps more often as associated illnesses observed during pleurodynia epidemics (see Aseptic Meningitis below)

Diagnosis A clinical diagnosis is seldom difficult once the existence of an epidemic is apparent However during the early stages of an epidemic or when only sporadic cases are encountered the occurrence of severe pain in the chest or abdomen may suggest serious medical or surgical emergencies This impression is often reinforced when the disease occurs in older persons perhaps with a previous history of cardiac disease or in children when attended by fever nausea and vomiting Fortunately in the former instance the moderately elevated but otherwise normal pulse plus the *shifting character* of the pain will suggest the proper diagnosis In the latter instance the absence of deep seated tenderness the presence of superficial hyperesthesias of the skin and the usually early remissions of pain are helpful in *differentiating* pleurodynia from acute appendicitis Since herpangina may also be prevalent and in children may be characterized occasionally by abdominal pain careful inspection of the pharynx and faucial areas will be helpful in making a correct clinical diagnosis It should be noted however as described below that certain Coxsackie B viruses can cause severe sometimes fatal myocarditis in the newborn

Laboratory diagnosis is made by demonstrating Coxsackie group B viruses in the stool or throat washing taken during or shortly following the acute illness A rise in specific neutralizing antibodies against one of the group B viruses during the illness and convalescent periods provides evidence for infection concomitantly with the illness As with the group A viruses the complement fixation test for antibodies although apparently group specific may give nonspecific reactions within the Coxsackie group and is chiefly of use in confirming that a Coxsackie infection occurred

Prognosis and Treatment Despite its sometimes stormy course virtually no deaths have been attributed to the uncomplicated disease There is no specific treatment for the disease or its complications Modern antimicrobial drugs are ineffective against the Coxsackie viruses Symptomatic relief from pain and high fever usually can *be achieved by analgesics and antipyretics* Opiates are occasionally required to alleviate severe pain Rest in bed is of course mandatory during the period of pain and fever Too rapid return to normal activity seems associated with more frequent sequelae particularly orchitis and meningeal disease

ASEPTIC MENINGITIDES" DUE TO COXSACKIE AND ECHO VIRUSES

Certain Coxsackie and ECHO viruses represent the most recently established causes of this clinical syndrome an entity already *characterized by the variety of its multiple* causations No less than eleven Coxsackie and ECHO serotypes have been incriminated (see table) At least ten other distinct infections (see Nonpurulent Meningitis p 175) are associated with aseptic meningitis the most common of which are nonparalytic poliomyelitis (three serotypes) mumps lymphocytic choriomeningitis and herpes virus infections It is now apparent that Coxsackie and ECHO virus infections together with nonparalytic poliomyelitis are responsible for a large number of the aseptic meningitis cases observed in infants *and young children* whereas other agents are more likely to be responsible in adults The epidemiology of aseptic meningitis due to enteroviruses is similar to that of polio

myelitis herpangina and epidemic pleurodynia

Clinical Manifestations Aseptic meningitides due to ECHO and Coxsackie viruses are clinically indistinguishable from each other and also from nonparalytic poliomyelitis (see Poliomyelitis p 63) Rhodes reviewed the clinical features of eighteen cases of aseptic meningitis due to Coxsackie B viruses observed from 1951 to 1955 "The average age was 6 years (range 3 to 11) The clinical features consisted of fever signs of meningitis nausea and vomiting headache drowsiness and pain in the neck and back in most cases" Although seven patients complained of myalgia none had signs of meningitis nausea and vomiting or paralysis Only two patients had cerebrospinal fluid cell counts higher than 500 per cu mm the average was 188 cells per cu mm Sugar and chloride values were normal and protein values did not exceed 45 mg per 100 ml

Diagnosis The clinical diagnosis of the aseptic meningitis syndrome is considered in the sections on Nonpurulent Meningitis p 176 and Poliomyelitis p 64 A specific etiological diagnosis of Coxsackie or ECHO infection depends on isolation of the causative agent (usually from throat or stool specimens) and the demonstration of an antibody response in complement fixation or neutralization tests At times the agent may be isolated directly from the cerebrospinal fluid

Pathology No uncomplicated cases of aseptic meningitis due to Coxsackie and ECHO viruses have been reported at autopsy however several fatal cases of myocarditis neonatorum" due to Coxsackie B viruses types 3 and 4 also showed cerebral lesions Two of these cases had pathological signs of aseptic meningitis and two of focal encephalitis Kibrick describes one case in which the spinal cord and meninges revealed edema and a diffuse infiltration with moderate numbers of macrophages and occasional polymorphonuclear leukocytes Areas of encephalitis were seen in the cerebellum and pons and degenerative and inflammatory lesions were particularly numerous in the spinal cord involving the anterior horns and reticular formations"

Prognosis and Treatment Coxsackie and ECHO virus meningitis is apparently uniformly nonfatal (after the neonatal period) having a more benign and shorter course than other forms of aseptic meningitis Although less common the illness tends to be somewhat more severe in adults

Because it is impossible to exclude the presence of polioviruses or other more severe viral infections of the central nervous system during the acute stage of illness treatment perforce must follow that prescribed for the preparalytic period in poliomyelitis (see p 65) Prognosis for the same reason must be guarded

EXANTHEMATA AND "ASEPTIC MENINGITIS WITH RASH" DUE TO ECHO VIRUSES

In 1954 Neva and Enders reported a new virus now classified as ECHO 16 in association with a benign rash disease subsequently called "Boston exanthem" The same virus was later found in relation to a similar outbreak in Pittsburgh No central nervous system involvement was observed in either outbreak During the first outbreak in Boston however ECHO 16 was also found by Kibrick in eight hospitalized persons with aseptic meningitis none of whom had rash

In 1956 a widespread epidemic illness occurred on the continent of Europe in England and in Canada described variously as meningitis with rash" epidemic exanthem with meningitis" and "lymphocytic meningo encephalitis with myalgia and rash" ECHO 9 virus was recovered from each of these outbreaks as well as from a previous outbreak in Italy in 1955 (aseptic meningitis without rash) and a subsequent one with rash in Wisconsin in 1957

The illness as generally observed appeared to fit the picture of uncomplicated viral meningitis and the associated rash which usually appeared one to three days after onset of fever was described in some cases as maculopapular and rubelliform and in other cases as blotchy and morbilliform vesiculation followed some of the more severe eruptions No deaths were observed

The ECHO 9 virus strains associated with these outbreaks were isolated both in monkey kidney cultures and in suckling mice and were reported variously in different studies as ECHO virus and as a new Coxsackie A virus However since all the strains isolated seem identical with a virus already classified as ECHO 9 this term is most generally used

MYOCARDITIS NEONATORUM

(*Epidemic Myocarditis of Newborn Acute Aseptic Myocarditis*)

Evidence that Coxsackie B viruses types 3 and 4 may produce severe even fatal myocarditis in the newborn was presented

in several excellent reports appearing in 1955 and 1956 Fourteen fatalities were observed in a total of twenty cases reported from Southern Rhodesia Amsterdam and Boston In most cases infection undoubtedly occurred after birth however several infections may have occurred *in utero* Pathological examination revealed diffuse and focal myocarditis characterized by degeneration of myocardial fibers and infiltration by macrophages and leukocytes Aseptic meningitis and focal encephalitis were also observed in several fatal cases

PREVENTION OF COXSACKIE AND ECHO VIRUS INFECTIONS

The success of the Salk poliomyelitis vaccine offers hope that effective Coxsackie and ECHO vaccines can be produced However the need and demand for them are as yet undefined

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Poliomyelitis

(*Infantile Paralysis*)

Definition Poliomyelitis is a common acute viral disease characterized clinically by a brief febrile illness with sore throat headache and vomiting and often with stiffness of the neck and back In many cases a lower neuron paralysis develops in the early days of illness

History References to conditions which may have been poliomyelitis date from earliest times but no descriptions of this disease have been found in medical literature before the end of the eighteenth century At this time mention of acute paralysis in childhood was made in England by Michael Underwood in his textbook on diseases of children During the subsequent fifty years there were several descriptions of poliomyelitis the best being that by the German orthopedist Heine which was published in *1840* During most of the nineteenth century the disease was regarded as a sporadic and ubiquitous affliction of young infants Its contagious and epidemic character did not receive emphasis until Medin s work appeared in Sweden in 1890 From that time forward the disease ceased to be a curiosity and became a periodic scourge in some countries The principles of its epidemiology were first reviewed by Medin s pupil Wickman who published his monograph in 1908 the same year in which Landsteiner discovered the virus

Etiology The virus of poliomyelitis has been commonly isolated from patients acutely ill with this disease the best sources being intestinal excreta the oropharynx occasionally the blood and at necropsy the central nervous system It is extremely small as viruses go It is labile in some respects being sensitive to drying and heat at pasteurization temperatures and stable in others resisting ether and certain other so called disinfectants The virus remains viable at icebox temperature in aqueous suspensions of feces for months and in pieces of infected spinal cord for years when stored in 50 per cent glycerol

Man is the animal most susceptible to the virus chimpanzees and cynomolgus monkeys come next and after these come the other primates However infection of mice and other rodents has been achieved particularly with Type 2 strains A fundamental discovery by Enders Weller and Robbins (1949) has been the demonstration that polioviruses will grow in tissue culture and give rise to cytopathogenic changes whereby their presence can be recognized As a result of the practical application of this method the isolation typing neutralization antigen and vaccine production of polioviruses are almost universally carried out *in vitro*

Within the poliovirus family there are three immunological types (1 2 and 3) It has been shown repeatedly in the laboratory that although *type specific immunity* can be induced an animal can be reinfected and paralyzed with an *heterologous* type of poliomyelitis virus This is the reason usually given to explain why the same person may contract paralytic poliomyelitis more than once Repeated subclinical or inapparent infections due to the same type of poliovirus may and probably do occur quite often in man

Epidemiology and Pathogenesis Poliomyelitis is an endemic and epidemic disease of world wide distribution primarily affecting children and spread by *contact* with clinical and inapparent "cases acting as carriers Although regarded as a contact disease there is still much to be learned as to how this disease is actually transmitted Some of the present mystery vanishes however with the recognition that unlike certain other contact diseases such as measles in which the disease passes from one recognized case to another the spread of poliomyelitis often occurs through the medium of mild cases many of which are so mild as to escape recognition Evidence is convincing that during an average epidemic of poliomyelitis those who are ill enough to be diagnosed or become paralyzed represent a small fraction of those who become infected Nevertheless the contact theory does not cover the whole story for it does not explain why cases of poliomyelitis occur at a much higher rate in the summer and early autumn than in the winter There are two possible explanations either something happens in summer which enormously facilitates the dissemination of the virus throughout a community or something happens which makes people far more susceptible

Poliomyelitis virus has been found under natural circumstances in sewage and on food (contaminated by flies) and in flies and cockroaches during epidemics An obvious question is whether the patient s immediate or remote environment is not only contaminated but infectious serving to spread the disease through the agency of contaminated water food or insects However there is at least no evidence that insects are an *essential* link in the chain as are mosquitoes in the transmission of malaria or yellow fever

Children are more susceptible to poliomyelitis than are adults As in measles this is an expression of acquired immunity on the part of the adult populations The age at which this immunity is acquired differs in different places In the United States although most of the cases fall within the age group of four to fifteen some 25 per cent or more of the cases now occur in young adults and this percentage is rising

How the virus of poliomyelitis actually enters the human body is a subject of controversy It is unlikely however that it gains access to the central nervous system directly by way of the nasal mucosa and the olfactory bulbs It is more likely that it penetrates through the mucosa of the oral cavity the alimentary tract or conceivably the skin Very early in the disease or late in the incubation period the virus has been recovered from the blood stream but the central nervous system the oral cavity and the intestinal tract are sites for which it has affinity and where it soon settles (see Fig 12)

Prior to during and after an acute attack virus can be demonstrated in the oropharynx and in the intestinal tract in the former site it persists for about ten days from onset and in the latter for about three to six weeks or even longer This (acute and convalescent) carrier state can be initiated by an attack so mild as to go undiagnosed or even unnoticed Although usually not more than one person in a family becomes paralyzed at a single time simultaneous multiple infections within families are common Evidence suggests however that in certain families a high prevalence of the paralytic form of the disease has prevailed through several generations

As to *predisposing influences* recent tonsillectomy (performed within three months of onset) is regarded as one During epidemics this operation has been followed by bulbar poliomyelitis more often than might be expected Furthermore such minor procedures as inoculations for diphtheria or pertussis also fall into this category Severe exertion or stress or an injury if sustained on the day or two preceding or following the onset of acute poliomyelitis tend to make the prognosis less favorable Pregnant women are quite vulnerable to poliomyelitis They are also subject to higher than average rates of exposure when there are young children in the family

Morbid Anatomy Important lesions occur in the central nervous system notably in the gray matter of the spinal cord Hyperplasia of lymph nodes (cervical axillary and mesenteric) also occurs Myocarditis has been described in fatal cases

Classic *neural* lesions are the result of

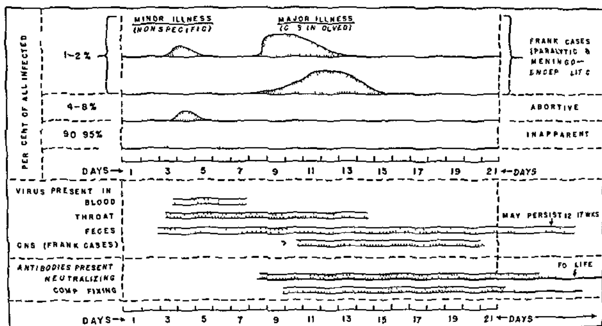


FIG 12 Upper panel Diagram illustrative of various clinical forms which poliomyelitis may assume The stippled areas indicate periods of fever The time scale in days starts with the hypothetical day of exposure
Lower panel The presence of virus and antibodies as related to the clinical course of the infection

the neuronotropic character of the virus Ganglion cells in the anterior horns of the spinal cord are characteristically involved particularly in the cervical and lumbar regions These lesions pass through stages marked by diffuse chromatolysis destruction of neurons neuronophagia and perivascular and interstitial infiltration of round cells The brain stem is nearly always involved in fatal cases whereas lesions of the cerebral cortex are restricted to the precentral gyrus (motor area)

Pathological Physiology Although physical signs attributable to a disturbance with in the central nervous system can often be explained on the basis of a *diffuse* inflammatory reaction in acute poliomyelitis a correlation between direct nerve cell injury and the physical sign should be considered first before incriminating the accessory influences of edema or other secondary factors Since muscular function is often regained in previously paretic muscles during convalescence this would seem to indicate that the changes in certain virus infected cells are *reversible* Illustrative of the reversible affections are the transient paresis of the urinary bladder and the intestinal tract

The occurrence of spasm in paralytic and nonparalytic muscles has been the subject of extensive discussion Some investigators consider it to be due to increased myotatic reflex activity others to reflex contraction secondary to pain in hyperirritable muscles

Incubation Period Usually stated as about ten days the incubation period is actually less It may range from as short as three to as long as thirty five days Average figures indicate nine to thirteen days for paralytic cases and three to ten for abortive cases the difference being that first phase symptoms may be so slight as to escape notice Opinions differ as to the best method of dating the onset of the disease It is the writer s practice to consider the earliest (*first phase or minor illness*) symptoms when present as marking the onset of the disease

Symptoms Common clinical forms which poliomyelitis may assume are illustrated in Figure 12 Clinical terms for the designation of various forms of infection with polioviruses have included the following *inapparent infection* (alimentary infection) which is the commonest form of infection with polioviruses and is diagnosable only with the assistance of laboratory tests *abortive poliomyelitis* a somewhat nonspecific term indicating that although the infection did not progress beyond the minor illness the clinical and/or laboratory evidence was sufficient to warrant a diagnosis of poliomyelitis *paralytic poliomyelitis* which may be of the spinal bulbar

or cranial nerve types * and *encephalitis due to polioviruses* Previously the term of *nonparalytic poliomyelitis* was employed but a recent recommendation from the World Health Organization (1957) has called for its elimination and the substitution of *aseptic meningitis* qualified as follows (poliomyelitis probable) or (etiology unknown) or (due to poliovirus type 1 2 or 3) or (due to mumps Coxsackie or ECHO viruses etc) For the identification of the last named infections laboratory tests are required By this nomenclature cases of proved poliomyelitis with the diagnosis confirmed in the laboratory will be so recorded and cases of unproved etiology will *not* be designated as poliomyelitis unless the clinical indications are very strong Those which are due to other agents will perhaps be more properly recorded The necessity for this change stems from the fact that prior to the wide scale use of the Salk type vaccine in the United States not more than 50 per cent of so-called nonparalytic cases of poliomyelitis were actually poliomyelitis It is possible that a still higher percentage will be erroneously designated if the loose term "nonparalytic poliomyelitis" continues to be used

"The Minor Illness " These brief illnesses so commonly seen during poliomyelitis epidemics usually last only 24 hours and are more frequent in children than in adults They are the clinical indications that infection has started and are probably contemporaneous with the period of viremia but they cannot be diagnosed with certainty by clinical methods Clinical manifestations include fever headache vomiting listlessness sore throat and rarely diarrhea Sore throat is a much more frequent complaint in the *minor* as opposed to the *major* illness and thus becomes a useful symptom in determining the stage of the disease The cerebrospinal fluid findings are almost always normal here and the symptoms comparable to those of a variety of mild acute illnesses A tentative diagnosis can be made however on those patients who have been in close association with a recognizable case of poliomyelitis For a positive diagnosis virus isolation or antibody tests are almost essential

The minor illness in poliomyelitis may or may not be followed by the major illness In the latter event it is also known as *abortive poliomyelitis*

The "Major Illness This term relates to aseptic meningitis and paralytic poliomyelitis It designates that important complication" of acute poliomyelitis which may occur with or without antecedent symptoms and which indicates that lesions have developed within the central nervous system to an extent sufficient to give rise to neurological symptoms The onset may be abrupt or gradual over a period of several days If the onset is sudden fever vomiting and severe headache are again commonly encountered These early symptoms may be accompanied or followed quickly by spontaneous pain in the extremities—deep pain hyperesthesia and sometimes paresthesia Soreness and stiffness of the neck and back and hamstring muscles become prominent early Severe lumbar back pain not associated with motion of the spine (in fact relieved by motion) is relatively common in adults with severe infections Abdominal pain may also occur

If "major illness" symptoms develop insidiously as is often the case with adults there may be no fever at first or only slight fever not above 100° F This gradual onset may be puzzling and responsible for a delay in diagnosis Such patients appear uncomfortable and restless rather than sick They complain of listlessness intermittent headache anorexia with occasional vomiting pains in the extremities and again hyperesthesia and paresthesia followed by stiffness of the neck and back and pain in the back

During the febrile period temperatures may range from 100 to 103 F depending on the age of the patient and may last three to ten days The onset of weakness or flaccid paralysis usually occurs while fever is still present but may appear as the fever begins to fall Thus concurrently with an improvement in the systemic clinical picture the patient discovers that his limbs will not function properly Acute retention of urine is not uncommon particularly when severe paralysis of the lower extremities is present Constipation or obstipation is also common

Spinal Paralytic Poliomyelitis This is the classic form of poliomyelitis in which the presence of flaccid paralysis makes the clinical diagnosis quite definite Muscles commonly paralyzed in order of frequency are those of the legs (by far the most frequent) arms back thorax face intercostal region and diaphragm

* A clinical definition of *paralytic poliomyelitis* is that the patient must have clearly demonstrable paralysis as opposed to transient weakness This paralysis of the flaccid type should be recognized preferably by more than one physician on two consecutive physical examinations performed at least 24 hours apart or better still during the acute stage of the illness and during convalescence

Respiratory Paralysis Difficulty in breathing results from several causes which will be considered later

Encephalitic Symptoms These occur at any stage and in some epidemics are very frequent Symptoms include dizziness which is not a true vertigo but rather a lightheadedness apprehension yawning twitching of the limbs and irritability followed by lassitude drowsiness and even coma Convulsions are rare

Bulbar Paralysis The bulbar form is most serious It includes those cases in which cranial nerve nuclei are involved When the tenth (and often the eleventh) cranial nerves are implicated there is unilateral or bilateral weakness of the soft palate which sags unnaturally in the back of the throat There may also be weakness of the pharynx and vocal cords This results in an inability to swallow or to talk clearly and ocasionally in regurgitation of fluid through the nose Other patients have symptoms and signs indicating involvement of the autonomic centers of the medulla notably the respiratory center Respiratory failure may progress with great rapidity

Diagnosis Initial symptoms and signs of the acute disease are likely to be nonspecific Often a preliminary diagnosis is tonsillitis or summer grippe An important point of differentiation is that signs indicating respiratory tract involvement other than sore throat are absent If the disease progresses stiffness of the neck back and hamstring muscles soon becomes prominent At this stage there is apt to be an increase of cells and protein in the cerebrospinal fluid These clinical and laboratory findings are again not specific for poliomyelitis being essentially those of a benign aseptic meningitis which may be due to a variety of agents of viral bacterial spirochetal or even protozoan origin Thus it may not be possible to make a positive diagnosis of aseptic meningitis (due to poliovirus) without resort to virological or immunological tests In the absence of such tests the term aseptic meningitis (poliomyelitis suspected) is recommended

Nevertheless stiffness of the back is a characteristic sign of poliomyelitis It is best elicited with the patient sitting up in bed with the knees naturally flexed and asking him to "kiss his knees If the back is stiff attempts to do this will cause pain Tightness and soreness of the hamstring muscles and resistance to extension of the leg are common

The *reflexes* in early stages of the "major illness may be normal and active Later if the onset of paralysis is imminent there is an irregular shift of hyperactivity and then sudden (and sometimes transient) shifts to diminished (or absent) reflexes Usually the appearance of reflex changes precedes the appearance of weakness or paralyses by twelve to twenty four hours Superficial reflexes *i e* the abdominal cremasteric and spinal reflexes are the first to disappear

Although the periodic but cautious examination for muscle power is part of the daily examination of the patient ill patients should be spared from exhaustive and exhausting muscle examinations during the acute stage of the disease Patients in whom there is progressive muscle weakness however require frequent observation for evidence of diminished excursions of the intercostals and diaphragm

A valuable laboratory test is the examination of the *cerebrospinal fluid* If the (white) cell count is elevated above 8 cells per cu mm and the protein is above 35 mg per 100 ml the diagnosis in a suspicious case is more likely but one cannot rely on a negative test to exclude poliomyelitis Furthermore there is an element of timing because during the minor illness a normal cerebrospinal fluid is to be expected One should also recall that these positive findings are those of aseptic meningitis of other etiology The cerebrospinal fluid cell count is likely to be highest during the first week of the major illness and although the predominant cell type is usually mononuclear early in the disease polymorphonuclear forms predominate Usually the white cell count does not exceed 300 cells per cu mm The protein content of the fluid is low and often normal during the first week but rises later remaining up through the fourth week and then gradually decreasing to normal Thus a high and rising protein content may exist after the cell count has returned to normal a picture often confused with the Guillain Barre syndrome

There is no consistent change in the peripheral *blood picture* As a rule the total leukocyte count is only moderately elevated (10 000 to 16 000 per cu mm) with a relative lymphopenia Rapid erythrocyte sedimentation rates have recently been reported in about half the patients tested Routine *urinalysis* reveals no abnormalities For the isolation of poliovirus tissue culture techniques are now available in many laboratories Stool specimens are usually the best source of virus

Serological tests (neutralization and com

plement fixation tests) which can be done on matched (early and convalescent) blood samples for purposes of clinical diagnosis are becoming of increasing value Their availability is likely to increase

Differential Diagnosis Paralytic poliomyelitis should be considered whenever flaccid paralysis (particularly paralysis without sensory changes) occurs in the presence of fever and in the absence of traumatic or other types of injury to the cord It can be confused with the summer arthropod borne encephalitides but serious paralysis of the limbs does not usually occur in those conditions

Poliomyelitis without paralysis (aseptic meningitis) offers great difficulty in diagnosis without the aid of laboratory tests This picture can be confused with *mumps encephalitis* particularly when mumps occurs without involvement of the salivary glands and with *postmeasles encephalitis meningoencephalitis* (of undetermined type) *lymphocytic choriomeningitis* and *infectious neuronitis* (Guillain Barre syndrome) Infections by members of the Coxsackie group and ECHO group of viruses may be easily mistaken for poliomyelitis as may also leptospirosis

Rheumatic fever is often diagnosed as poliomyelitis Other conditions which have been confused are *acute meningitides* (of various types) and *tuberculous meningitis* In these conditions the diagnosis is likely to become apparent in the course of time More rarely *acute osteomyelitis trichinosis acute appendicitis infectious mononucleosis* and *lead poisoning* are mistaken for poliomyelitis

It is also well to recall that generalized weakness of limbs may occur in the presence of acute fever as in influenza or acute enteritis

Prognosis During the early and acute stage of poliomyelitis predictions as to eventual outcome are risky Extreme agitation restlessness and apprehension in the febrile stages may indicate a poor prognosis and if physical exertion has been undertaken in the early days of illness (in the major illness) a less favorable result can be expected The height of fever bears little relationship to the extent of paralysis which may ensue but the duration of high fever may be significant

The *mortality rate* for any given epidemic will vary according to diagnostic criteria It may range from 1 to 1 per cent or higher By far the highest mortality occurs in bulbar cases The severity of the illness and the case fatality rate increase with the age of the patient

Paralysis shows a remarkable tendency to improve in this disease but the *extent of recovery* is subject to variables and primarily to the degree of irreversible change which the virus has inflicted on the infected nerve cells

The rate of recovery of strength in individual muscles or muscle groups follows a fairly definite pattern By the end of the third month from the onset a muscle will usually recover approximately 60 per cent of the total strength that it will ever recover under treatment During the next three months an additional 20 per cent may return After this the recovery rate becomes increasingly slower so that by the end of eighteen months of treatment it is more than likely that little increase in muscle strength can be expected

Treatment At present no specific treatment is available for poliomyelitis None of the antimicrobial drugs which have been tried has any effect in destroying the virus or controlling its spread within the body

Guiding principles of therapy depend upon the type of case the mild case without paralysis the paralytic case and the life threatening case Only in the latter two will the services of specialists be required In the life threatening case adroit management and a team of specialists may be necessary

Mild Cases It is impossible to determine within the first few hours or days of illness whether a given case will or will not go on to the eventual development of paralysis But the clinician s responsibility in the management of these early though potentially severe cases seems clear Thus *during epidemics* all patients with brief febrile illnesses of the type described above deserve to be regarded with suspicion physical activities should be curtailed and the patient should be kept quiet and in bed under observation preferably at home for at least a week Seldom do they require special types of therapy such as drugs hot packs orthopedic care or physiotherapy Potentially such patients may be infectious and therefore require some degree of isolation In a small percentage of these patients some degree of paralysis usually mild may develop during the postfebrile stage For this reason such patients should be followed for at least three weeks

Paralytic Cases Hospitalization is advisable for paralytic cases An isolation hospital is not necessary for general hospitals

can care for poliomyelitis patients provided isolation precautions can be carried out Care should be exerted that the trip to the hospital involves a minimum of exertion and trauma Within a large hospital the management of a patient with acute and advancing paralysis often involves the services of a team composed of a physician (internist or pediatrician) an orthopedic surgeon a physiotherapist and perhaps specially trained nurses

GENERAL MEASURES FOR THE CASE WITH MYELITIS Orthopedists recommend that a hard bed be provided from the beginning The bed should be fitted with a footboard placed several inches beyond the mattress allowing room for the heels or toes when the patient lies supine or prone If the legs are weak the knees should be supported in a slightly flexed position weak arms should be in external rotation alongside the body but not against it

Early in and during the stage of active myelitis (in which fever is usually present) there are four important aspects of general therapy adequate rest cautious use of sedation and analgesia adequate fluids and proper nursing care

For all patients whether at home or in the hospital *early bed rest* is important As part of the program of rest the patient should be spared from extensive and repetitive physical examinations undue fatigue and from injections which are not essential

Sedation and other means for the relief of pain are important considerations Relief may be aided by the intermittent application of hot moist packs Numerous types of these packs have been advocated Two general types are in current use the so called wrap around pack and the 'lay on pack Woolen cloth is favored material Both types of pack call for application directly to the skin of the hot wet wool from which the water has been well wrung This is then covered by two additional layers one of which is of waterproof material and the second is for insulation

The response to common analgesics and sedatives is not very satisfactory in early stages but sedatives are often used Often if pain is relieved by hot packs drugs will not be necessary This is desirable for the danger of aggravating incipient or actual respiratory difficulty makes it necessary to use sedatives cautiously

Although several drugs have been advocated for the relaxation of muscle tightness and relief of pain it would seem that they are not as effective as the more cumbersome method of hot packs

Fluid should be given freely and whenever hot packs or hot baths are used salt tablets should be added to make up for excessive salt loss in perspiration

Nursing care for the acute disease should follow general principles used in acute infections The diet should be light Isolation technique with so called typhoid precautions should be followed for one to three weeks depending upon local rules The patient s stools should be disposed of as quickly and safely as possible The use of a chemical disinfectant to sterilize the stools is not recommended

CARE OF PARALYZED LIMBS Protection of the recently paralyzed limb (rather than fixation) is the objective The ultimate care of such limbs is essentially an orthopedic problem and consequently will not be discussed here

COMPLICATIONS *Urinary retention* is common in patients with severe involvement of the lower extremities Before resorting to catheterization an adequate trial of drug therapy should be given The parasympatheticomimetic drug furfuryl trimethylammonium iodide (Furmethide) has proved efficacious if given subcutaneously in adequate dosage In infants doses of 1 25 mg (0 3 to 0 5 ml) have been used In children the dose has ranged from 2 to 5 mg in adults from 5 to 7 mg If there is no response catheterization is indicated together with prophylactic antimicrobials In general urinary retention is a complication that lasts but a few days

Life Threatening Poliomyelitis BULBAR POLIOMYELITIS Loss of ability to swallow is the most common cause of respiratory tract obstruction in poliomyelitis patients Steps involved in treating this condition begin with *postural drainage* to maintain a free airway with the bed tilted at an angle of 10 to 12 degrees off horizontal Patients are usually more comfortable in a side lying than a prone position When mechanical aspiration is done a rubber or polyethylene catheter may be passed through the nose into the hypopharynx The catheter is then connected to an electrically driven suction machine or water pump the ideal is to provide gentle intermittent suction If swallowing is impaired fluid *salt and nutriments are administered* either by hypodermoclysis intravenously or by proctoclysis The amount of fluid depends on the age size and condition of the patient 3000 ml or more are recommended daily for adults Intravenous saline and glucose should be given *slowly and in small* amounts not more than 500 ml at a time

Respiratory difficulty may reflect at least four types of disturbances In any given case of poliomyelitis several of them may coexist but it is important to recognize which are involved They are (1) Disturbance of function of the muscles which perform the respiratory movements (2) Disturbances of the central control of respiration so that damaged neurons do not respond in the normal manner to changes in the CO concentration pH and O saturation of arterial blood (3) Obstruction of the airway caused by inability to swallow and by paralysis of intrinsic muscles of the larynx aspiration of oral secretions may lead to atelectasis of portions of the lung and further loss of respiratory function (4) Pulmonary edema which may occur when extensive bulbar disease is present It brings about serious impairment of gas exchange in the lungs

In estimating the condition of the respiratory muscles the appearance of the patient is extremely important With mild degrees of respiratory muscle weakness the patient exhibits anxiety by facial expression restlessness irritability emotional lability and wakefulness With more weakness of the respiratory muscles the face becomes flushed hypoxia and CO retention increase pallor replaces the florid appearance there is inability to cough and respiration becomes rapid and labored with the use of accessory muscles Certain clinical and laboratory procedures have proved of value in estimating the adequacy of the respiratory muscles The strength of intercostal muscles is tested by having the patient expand the chest against manual pressure exerted against the lower portion of the rib cage Intercostal muscles are also tested by restriction of the diaphragmatic excursion by manual force supplied to the upper part of the abdomen As sniffing is brought about by descent of the diaphragm ability to carry out this action constitutes a test of diaphragmatic function The resting small child with normal respiratory muscle function is able to hold its breath for fifteen to twenty seconds the child suffering from respiratory muscle impairment of relatively slight degree falls far short of this Under certain circumstances a fluoroscopic examination to test diaphragmatic excursion is useful furthermore a spirometer should be used for accurate measurement of ventilatory exchange

RESPIRATORY AIDS When only a small loss of function of respiratory muscles is present there is no need for mechanical aid to respiration However when respiratory muscles are so impaired that conscious effort is necessary to supplement their action and this compensation does not appear adequate then mechanical therapy is necessary One of the factors indicative of respiratory inadequacy is the inability of the patient to obtain sleep It is a mistake to wait for signs of hypoxia or CO accumulation before using mechanical therapy for they represent signs of respiratory decompensation In the use of mechanical aids to respiration the general principle is that the patient s possible needs must be anticipated and unexpected crises should be avoided The patient s needs are best determined by following his vital capacity at regular intervals A rapid fall in the vital capacity to levels below one fourth of the resting normal value almost always indicates the need for mechanical aids in ventilation Every effort should be made to allay the patient s anxiety and emphasis should be placed upon the usually successful outcome The apparatus to be used should be at hand and obviously members of the medical and nursing staff should be familiar with its operation

For severe degrees of respiratory muscle weakness the *tank respirator* is the apparatus of choice When relatively minor degrees of respiratory muscle weakness exist the cuirass respirator and the rocking bed may be employed to give rest and sleep In general however both of these machines are of greatest use in the recovery period and in weaning patients from the tank respirator period In the United States positive pressure devices seem to have been less well suited for prolonged use and are probably most valuable as an adjuvant for the tank respirator period The main use of the *electrophrenic respirator* is in the treatment of respiratory impairment due to injury to the respiratory center

For initiating the use of the tank respirator it should be appreciated that since respirator patients no longer control their respiratory rate they often attempt to breathe voluntarily and out of time with the bellows By persistent instruction the patient is urged to relax and let the respirator do the work In general younger children are given a more rapid respiratory *rate* than older children or adults but the rate should be determined by clinical observation in steering a course between underventilation as opposed to hyperventilation with excessive loss of CO and alkalosis Of the two hyperventilation is by far the lesser danger Rates range from 30 per minute in young children to 18 per

minute in the adult Younger children are subjected to smaller pressure ranges than adults although some competent and experienced physicians do not follow this practice For small children an *intra tank pressure* starting at 0 and reaching —12 cm of water at its peak is suggested for the beginning 0 to —15 for older children and 0 to —18 for adults may be tried Some workers employ pressures which range from a positive reading of +3 or +4 to —18 The tidal exchange produced by each cycle of the respirator should be determined with a spirometer The respirator should then be set at a rate and pressures which assure a minute volume of respiration as close to the resting normal as possible In adults this is usually 6000 to 8000 ml A decrease in tidal air and minute volume with constant intra tank pressures is often a valuable indicator of early interference with respiratory exchange in the lungs which is usually associated with obstruction of the bronchial tree Signs of improvement which indicate successful action of a respirator include improvement or disappearance in the signs of anoxia such as restlessness pallor or cyanosis acceptance of the rhythm of the respirator and cessation of voluntary respiratory movements with relaxation so that the patient may fall asleep

It should be appreciated that when respiratory difficulty is due entirely to weakness of the respiratory muscles the tank respirator is of great benefit When improvement is not quickly obtained complicating factors must be sought These include obstruction of the airway pulmonary atelectasis pneumonia or pulmonary edema

Nursing care required by the patient in the tank respirator is of a special type The patient s skin must be cared for fluid mineral and nutritional requirements must be met Excessive handling of painful extremities should be avoided although the patient s position should be changed if possible every two hours Physical therapy should be postponed until the patient has become well adjusted to the respirator *Infections of the upper respiratory passages*—bronchitis and pneumonia—are serious and must be treated promptly When pneumonia is present oxygen therapy is of value Atelectasis is also a serious complication Danger of its occurrence may be minimized by frequently changing the patient s position by obtaining maximum safe pulmonary ventilation by prevention of aspiration of secretions When atelectasis of any considerable degree occurs bronchoscopic drainage is usually necessary In the event of pulmonary edema oxygen therapy should be given When cardiac insufficiency is present digitalis and other measures to improve cardiac function are indicated If the difficulty is caused by *injury of the* medullary respiratory centers such patients nearly always require mechanical aids to respiration If the tank respirator fails the electrophrenic respirator may be used but certain difficulties in its use limit its value

Obstruction of the airway resulting from an inability to swallow may induce respiratory difficulties Not only does it interpose a barrier to the air entering the larynx and trachea but during inspiration the pooled secretions may be drawn into the trachea and bronchi The general principle of treatment is to provide a free airway by postural drainage and mechanical aspiration of the secretions in the pharynx This should be done if possible without trauma If this fails *tracheotomy* is performed providing an airway which cannot be obstructed A cooperative patient is less likely to require tracheotomy than a panic stricken one Adults and older children are less likely to need it than very young children Mechanical respiration is of no value in the treatment of respiratory tract obstruction

Differing views exist as to the *indications for tracheotomy* and there are no dogmatic rules It perhaps goes without saying that it should be performed if possible by one expert in the technique and not as a hurried last resort type of procedure

It is wiser to operate when there is doubt as to the advisability of further watchful waiting even though occasionally the subsequent course of the patient may prove that survival without tracheotomy would have followed A careful unhurried tracheotomy is neither mutilating nor dangerous

The particular type of anesthesia selected depends upon the emotional state of the patient In exceedingly frightened panicky adults and in children general anesthesia is desirable An endotracheal tube is passed and cyclopropane in high oxygen concentration is introduced via the tube Cyclopropane accords rapid induction and rapid release from anesthesia Local anesthesia is adequate in the more controlled adult During local anesthesia artificial respiration is maintained by the anesthesia machine through a pharyngeal airway using 100 per cent oxygen In either case artificial respiration with the anesthesia machine through the tracheotomy is continued as

the patient is returned from the operating room

The tracheotomy should be performed as high as possible *i e* just below the first tracheal ring so that the tube will be outside the respirator

For the first twenty four to forty-eight hours after operation the patient is given nothing by mouth Fluid and electrolyte balance is maintained by intravenous administration At the end of forty-eight hours feedings of a soft diet are carefully given by an attendant and over the next several days solid foods are slowly introduced

MANAGEMENT IN RESPIRATOR Once the tracheotomy is done a free airway can be maintained by repeated suctioning In general the patient is placed in the tank respirator postoperatively If the patient is able to maintain adequate respiration unaided he may be placed on the respirator bed with the respirator tank open and the bellows not operating In this situation artificial respiration may be instituted at a moment s notice

The respirator must be provided with an adjustable collar bar so that the tracheotomy is outside the respirator at all times

The next most important task is to maintain a clear airway First the physician must consider the tube itself The tracheotomy tube should be changed forty-eight hours after initial installation and weekly thereafter Second there should be ample opportunity for secretions to drain from both sides of the lungs This is accomplished by placing the patient in the Trendelenburg position every one to two hours for about twenty minutes and by turning him from side to side every two hours Intermittently he should be given a period on his back In the case of severe respiratory involvement the periods of Trendelenburg position may need to be lengthened Suctioning should be at frequent enough intervals to keep the airways free from secretions at all times The immediate postoperative period may require nearly constant suctioning

Weaning from the tank respirator should be instituted as early as possible when the patient is afebrile and as soon as he is able to do without the respirator for thirty to sixty seconds The tank respirator is gradually replaced by a simpler device *i e* a cuirass respirator or a rocking bed

Early Convalescent Care The aim in convalescent care is to restore the maximal functional capacity which is possible within the limits imposed by the actual damage to the nervous system It should be done with an awareness of the psychological impact on the patient which not only the illness but the therapy may have produced During the period of after-care and rehabilitation favorable conditions should be provided for the restoration of normal function and the preservation of the limbs in the best condition for late orthopedic operations if such become necessary Rehabilitation today calls for more than the care of limbs and should be directed from the start by physicians orthopedists and technicians

Prevention *Vaccination* against poliomyelitis is now an accepted procedure widely recommended The effective use of the Salk type formalinized vaccine has changed the picture of the control of poliomyelitis in a number of countries in which it has been widely used and particularly in the United States where vaccination of all persons within the ages of one year to forty or forty five years has been considered to be indicated In using this prophylactic measure one should recall that the Salk type vaccine does not prevent *infection* with poliovirus (*i e* inapparent or alimentary infection) but it does materially reduce the spread of poliovirus within the bodies of those who become infected In this fashion it lowers the incidence of *paralytic* poliomyelitis

Current techniques for the administration of Salk type vaccine call for its intramuscular inoculation in three divided doses of 1 0 ml each the second being given one month to six weeks after the first and the third not earlier than seven to nine months after the second There is as yet no universal agreement as to whether one or more "booster inoculations are desirable at intervals of a year after the last dose One indication for such inoculations is that the vaccinee expects to go to areas where the degree of exposure to polioviruses may be high such as the Middle East

There is little or no evidence that the Salk type vaccine acts as a provoking agent which might induce paralytic poliomyelitis for irritating allergic and other types of side reactions to the vaccine are uncommon and the contraindications to its use are few Young children with severe eczema are one group which might be omitted from vaccination programs

The decision to vaccinate individuals or a whole population during an epidemic or in the face of increased risk of exposure due to an advancing epidemic has both proponents and opponents In general opinions support the view that such "pre

minute in the adult Younger children are subjected to smaller pressure ranges than adults although some competent and experienced physicians do not follow this practice For small children an *intra tank pressure* starting at 0 and reaching −12 cm of water at its peak is suggested for the beginning 0 to −15 for older children and 0 to −18 for adults may be tried Some workers employ pressures which range from a positive reading of +3 or +4 to −18 The tidal exchange produced by each cycle of the respirator should be determined with a spirometer The respirator should then be set at a rate and pressures which assure a minute volume of respiration as close to the resting normal as possible In adults this is usually 6000 to 8000 ml A decrease in tidal air and minute volume with constant intra tank pressures is often a valuable indicator of early interference with respiratory exchange in the lungs which is usually associated with obstruction of the bronchial tree Signs of improvement which indicate successful action of a respirator include improvement or disappearance in the signs of anoxia such as restlessness pallor or cyanosis acceptance of the rhythm of the respirator and cessation of voluntary respiratory movements with relaxation so that the patient may fall asleep

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ber and variety of symptoms Most common is either a somnolent-ophthalmoplegic syndrome or an irritative hyperkinetic syndrome which may be choreiform or myoclonic Psychic disturbances may occur with symptoms ranging from mental impairment to those of the major psychoses Paralyses may develop and simulate poliomyelitis There is a fulminating type in which the patient may succumb within a few hours The fever may be slight or severe many afebrile cases have been noted Inapparent disease occurs and may lead to the appearance of parkinsonism

In the second or pseudopsychoneurotic stage there are many subjective complaints often without demonstrable objective findings of organic nervous disease Headache insomnia dizziness fatigability irritability and restlessness are common Such symptoms may persist for months or years after which the symptoms of the third stage appear Occasionally the third stage follows almost immediately upon the first

In the third or chronic stage peculiar motor vegetative and psychic symptoms make their appearance The disturbances of motility are like those of the Parkinson syndrome with or without tremor Among the more common vegetative disturbances are sialorrhea dacryorrhea and seborrhea There may be intellectual and emotional torpor

Diagnosis The diagnosis is difficult and the disease must be differentiated from the numerous encephalitides of established cause When the disease is epidemic and typical cases are occurring encephalitis lethargica may be suspected in puzzling cases of fever somnolence or delirium There are no laboratory procedures available which are helpful in confirming the diagnosis

Prognosis The case mortality rate varied in past epidemics but may have been as high as 20 to 30 per cent Among patients who survive a large number recover rapidly others are partially disabled for six months to two years still others are permanently disabled because of the severe symptoms of the third stage

Treatment Symptomatic and careful supportive treatment is all that is available In spite of claims to the contrary there is no evidence that any of the vaccines or serums used in treatment are of value

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St Louis Encephalitis

Definition St Louis encephalitis is a viral disease characterized by signs and symptoms referable to the central nervous system and its meninges It may occur either epidemically or sporadically

History In the summer of 1933 in and around St Louis more than 1000 cases of encephalitis occurred Muckenfuss Armstrong and McCordock and Webster and Fite demonstrated that the epidemic was caused by a virus previously unrecognized The malady is now endemic in America cases having been reported each year since 1933

Epidemiology This disease is one of the many arthropod borne virus encephalitides Certain species of mosquitoes have been shown capable of transmitting the infection The malady occurs most frequently during the summer and fall months No age is exempt but the highest incidence is in persons from fifteen to fifty years of age

Etiology The disease is caused by a small virus with dimensions of 20 to 30 $m\mu$ The virus is a member of the B group of arthropod borne viruses and is closely related to Japanese B Murray Valley West Nile and certain others It is also related to viruses of the Russian tick borne encephalitis complex which includes so called *Russian spring summer* or *Far East encephalitis* The agent has been propagated in media containing viable susceptible cells Mice and rhesus monkeys are susceptible hosts the former is the one of choice for the demonstration of virus in suspected material and for the performance of neutralization tests used in arriving at a diagnosis

Incubation It has been estimated that incubation periods range from four to twenty one days

Morbid Anatomy Edema vasular congestion and small hemorrhages are evident upon gross examination of the brain and cord Microscopic examination reveals an infiltration of the meninges with lymphocytes plasma cells large mononuclear elements and an occasional polymorphonuclear cell In the brain and cord are evidences of an acute inflammation *e g*

epidemic" vaccination is indicated if the evidence of imminent heavy exposure is adequate

General Procedures During epidemics it is well to seek the counsel of the local health officer so that a uniform plan for diagnosis and handling of patients may be adopted

Although the *isolation* of patients as usually practiced has not proved to be effective in controlling the spread of the disease it is reasonable to regard acute poliomyelitis patients as infectious for a period of ten to twenty days following onset Therefore early recognition isolation and reporting of cases are all important The period of *isolation of a patient with poliomyelitis* ranges from one to three weeks from onset depending on local rulings Mention has already been made of techniques to be followed in disposing of feces

Quarantine of an exposed family or intimate group of contacts although not of proved value seems wise particularly in the form of modified quarantine which calls for the restriction of familial juvenile contacts for seven to fourteen days

For *passive immunization* in unvaccinated individuals subjected to heavy exposure concentrated immune globulin (gamma globulin) may be administered in a dosage of 0 1 ml per pound of body weight

Certain measures have been found useful *during epidemics* These are (1) the *isolation in bed of all children with fever* pending diagnosis (2) the education in such techniques of bedside nursing as will prevent distribution of infectious discharges to others from patients isolated at home (3) the protection of children as far as practicable against unnecessary contacts with other persons and the avoidance of unnecessary travel and visiting especially of children during the high prevalence of the infection (4) postponement of elective nose and throat operations dental extractions or other types of induced trauma of appreciable extent

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Encephalitis Lethargica

(*Von Economo s Disease Epidemic Encephalitis*)

Definition Encephalitis lethargica is a malady which causes both degenerative and inflammatory changes in the central nervous system and is characterized by diversity of symptoms in different cases and in successive stages of the same case It is unfortunate that the name *epidemic encephalitis* has been used other types of encephalitis occur in epidemic form and encephalitis lethargica now occurs only sporadically

History The disease became known after a pandemic broke out in the winter of 1916–1917 Von Economo carefully described the disease at that time and called it 'lethargic encephalitis The first cases were seen in Rumania in 1915 Thereafter epidemics of the illness occurred in many parts of the world In 1918 it appeared in the United States After 1926 no further epidemics developed If the disease still occurs it is represented only by occasional sporadic cases

Etiology The cause of encephalitis lethargica is not known but there are reasons for thinking that the etiological agent may be a virus

Morbid Anatomy Hyperemia and minute hemorrhages may be present in the basal ganglia midbrain and pons Microscopically the lesions are of two sorts one degenerative the other inflammatory and infiltrative The degenerative process is characterized by destruction of nerve cells the inflammatory process by perivascular cuffing scattered patches of glial cell proliferation and lymphocytic infiltration Demyelination is not a prominent feature Lesions in the spinal cord are not marked

Symptoms The onset may be sudden or gradual Almost any type of neurological syndrome may be simulated there is a wide diversity of signs and symptoms The symptom-complex may be divided into three stages

In the first stage there are a large num

ceiving the injections met with "paralytic accidents" which at times resulted in death In 1907 Comby described a case with involvement of the central nervous system as a complication of jennerian prophylaxis Although isolated cases had been described from time to time it was not until the outbreak of postvaccinal encephalitis in England Holland and other countries in 1922 that attention was focused on them As the result of extended clinical pathological and experimental observations the tendency is to consider this type of nervous accident following in the wake of acute infections as a clinical entity

Epidemiology The disease has been shown to occur during the course of and after vaccination against rabies and smallpox and after measles German measles varicella mumps or influenza a few cases have been reported in which no history of a preceding infection was obtained The incidence varies from year to year being lower now after jennerian prophylaxis than it was in 1922 1925 It is not distributed uniformly throughout the population of a country nor are the inhabitants of all countries equally affected No age is exempt the malady occurs however more frequently in children than in infants and adults There is no evidence that the disease is contagious

Etiology The cause of postinfection encephalitis is not known nor has the malady been transmitted from man to experimental animals Three prevalent ideas regarding the etiology are (*a*) the viruses that cause the primary disease *e g* smallpox measles and so forth also give rise to the complicating encephalitis (*b*) a latent neurotropic virus is activated by the primary disease process (*c*) inasmuch as the encephalitis occurs during convalescence from some infectious malady or after vaccination certain workers have suggested that it is an expression of allergic phenomena There is no convincing evidence that any of these ideas is correct It seems unlikely however that the direct action of a virus is the cause of the disease because no virus is known to produce a perivascular demyelination similar to that seen in this disease Furthermore Rivers and his coworkers by means of repeated intramuscular injections of emulsions of fresh normal rabbit brain have produced a perivascular demyelination in monkeys manifested clinically by ataxia and paralyses This work has been confirmed and expanded

Incubation In view of the indecision regarding the etiology it may seem inappropriate to speak of an incubation period Regardless *of the cause of the encephalitis* there is a definite relation between it and the primary infections In postvaccinal encephalitis the "incubation" period in most instances lies between the ninth and thirteenth days In antirabic vaccination the encephalitis or myelitis usually comes during the second half of the Pasteur treatment or after it has been completed In measles the "incubation" period is not constant but as a general rule the encephalitis follows the appearance of the rash at variable intervals—usually it comes after the defervescence and at times the patient may have fully recovered from measles

Morbid Anatomy Pathological changes are found in both the white and gray matter of the brain and cord and are characterized by a minimal involvement of nerve cells and a perivascular infiltration or accumulation of cells accompanied by a destruction of myelin The perivascular collections of cells consist largely of altered glial elements many of which become phagocytic and take up large amounts of fat and degenerated myelin This pathological picture is decidedly unlike that seen in the encephalitides caused by viruses in many respects it is similar to that seen in acute multiple sclerosis and allied conditions

Symptoms There are two main types of the disease the encephalitic and the myelitic the former is more common in postvaccinal encephalitis the latter during antirabic vaccination while both types occur with almost equal frequency after smallpox Under such conditions it is to be expected that the clinical picture will vary and that the form it takes will depend on whether the brain or cord is predominantly involved

The onset of the disease if not abrupt is rarely insidious and is manifested in the encephalitic cases by pyrexia headache vomiting and drowsiness—cardinal symptoms "constantly present in severe and rarely absent in mild cases they may be the only symptoms present even in fatal cases Photophobia irritability delirium general or local convulsions trismus strabismus incontinence of urine extensive paralyses (spastic at first and then flaccid) or transient weakness of muscles incoordination and ataxia are symptoms that may occur Kernig s sign may be present the deep and superficial reflexes are variable In the myelitic cases symptoms caused by mild or severe involvement of the cord such as paralyses anesthesias paresthesias and disturbances of sphincter control are observed

The cerebrospinal fluid may be under in

vascular congestion small hemorrhages cellular infiltration perivascular cuffing degeneration of nerve cells neuronophagia and proliferation of glial elements

Symptoms The fact that the clinical picture varies tremendously can be explained upon the basis of differences in the severity of the infection and the localization of lesions in the brain and cord The clinical picture may resemble that seen in western equine Japanese B or Russian spring summer encephalitis According to Hempelmann the cases may be placed in three large groups

Group I Patients exhibit an abrupt onset without prodromal symptoms High fever nausea vomiting headache vertigo nuchal rigidity Kernig s sign lethargy difficulty with speech ataxia mental confusion and tremor of tongue lips or hands are the most common signs and symptoms Not all patients are lethargic paralyses are not common and when they do occur are usually of the spastic type involvement of the eye muscles is extremely rare The abdominal reflexes are usually absent while the deep reflexes tend to be exaggerated instead of diminished Constipation is common The pulse is usually proportional to the temperature but bradycardia may occur

The cerebrospinal fluid may be under increased pressure is free from bacteria and contains a normal amount of sugar an increased amount of globulin and an increased number of cells consisting chiefly of lymphocytes and other mononuclear elements The leukocyte count may be normal or show a moderate increase

As the patient s condition improves the temperature falls by lysis and in most instances reaches the normal level within seven to ten days in a few cases however the fever persists for four to six weeks

Group II In this group a stage of invasion lasting from one to four days and characterized by headache general malaise abdominal pains chilly sensations fever generalized muscular pains sore throat and a mild conjunctivitis accompanied by photophobia precedes the picture of encephalitis which after its development is similar to that described for Group I

Group III The third group consists of mild or abortive cases exhibiting only headache and fever of undetermined cause which would be missed in the absence of an epidemic and incorrectly diagnosed without the aid of a lumbar puncture

Diagnosis Clinical or pathological observations may lead to a diagnosis of encephalitis but usually do not serve to distinguish one type of viral encephalitis from another A specific etiological diagnosis may be made by laboratory procedures With specimens of serum taken during the acute phase and during convalescence neutralization hemagglutination inhibition and complement fixation tests may be of great aid in reaching a correct diagnosis

Prognosis From 5 to 30 per cent of patients die the mortality rate is reported to increase directly with age Those who recover do so quickly as a rule and are not usually bothered by troublesome or disastrous sequelae

Treatment Treatment is symptomatic No antimicrobial drugs have been shown to be effective

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Postinfection Encephalitis

(Acute Demyelinating Encephalitis Acute Disseminated Encephalitis Postvaccinal Encephalitis Postmeasles Encephalitis)

Definition Postinfection encephalitis is an acute malady of the central nervous system characterized by perivascular demyelination exhibiting itself as a rule in patients convalescing from infectious diseases particularly those caused by viruses or in those who are being vaccinated against viral maladies such as smallpox or rabies In certain instances the disease manifests itself in the absence of a history of preceding infection

History An involvement of the central nervous system may complicate the picture of smallpox and measles In 1874 Westphal recorded descriptions of pathological changes observed in the cords of patients who had died with nervous manifestations developing during an attack of smallpox and in 1886 Barlow and Penrose gave an account of a similar case that arose during the course of measles Soon after the initiation of vaccination against rabies it was realized that an occasional patient re

virus from a pigeon in similar circumstances These findings implicate birds in the epidemiology of the disease and explain its spread to widely separated areas Indeed it appears likely that the malady is primarily a disease of birds and that man and horses are accidental secondary hosts The studies of Kissling and his associates have greatly extended our knowledge of the role played by birds and mosquitoes in the epidemiology of the disease

Prevention Shahan and Giltner showed that a vaccine could be prepared by treating an emulsion of infective horse brain with formalin Although some evidence of protection was obtained with this preparation the results were not entirely satisfactory In 1935 Higbie and Howitt showed that the developing chick embryo could be infected with this virus In 1938 Beard Finkelstein Sealy and Wyckoff prepared a vaccine by formalinizing a suspension of infected chick embryo tissue Such tissues were found to contain a much higher content of virus than infective horse brain This material has been widely used Vaccination of horses and mules is achieved by subcutaneous injection at weekly intervals of two doses of 10 ml each of the vaccine of triturated chick embryo tissue treated with 0 4 per cent formalin Experimental and field studies have shown that this method is very effective Practical sanitary measures should of course be used such as screening stables and removing horses and mules from pastures after dark

THE DISEASE IN MAN

Meyer in 1932 described three cases of encephalitis in persons having contact with sick horses which he suspected might be due to the virus of the equine disease No proof for this suspicion was obtained however by biological test

During the summer of 1938 an epidemic of the *eastern variety* of the disease occurred among horses in southeastern Massachusetts During this time and in the same area an unexpected number of human cases of encephalitis occurred These were proved by Fothergill Dingle Farber and Connerley and by Webster and Wright to be caused by the equine virus by isolating the infectious agent from the brain tissue of fatal cases

There were about 40 human cases in this outbreak with a mortality of 65 per cent The majority of cases occurred in young children 70 per cent of them less than ten years of age During the summer of 1941 more than 3000 cases of the western type occurred in the north central states

Clinical Manifestations The onset of the disease was usually sudden particularly in young children The temperature rose rapidly to 103° to 105° F and generally remained at a high level during the course of the disease In some cases the disease was ushered in by a convulsion Repeated convulsions occurred during the course of the illness in many patients Deep coma occurred rapidly and persisted throughout the acute stage Nuchal rigidity stiffness of the back and positive Kernig s sign were usually present Many of the younger patients exhibited a peculiar edema about the face and upper extremities In some of the older patients the onset was more gradual

Laboratory Findings Certain laboratory findings were of importance particularly during the first few days of illness A leukocytosis was always present The cerebrospinal fluid was under increased pressure and contained an increased amount of protein and a normal content of sugar The cell count varied from 200 to 2000 per cu mm Of considerable importance was the fact that from 60 to 90 per cent of the cells were polymorphonuclear leukocytes

In fatal cases death occurred at variable times during the course of the disease most commonly during the first few days In the few patients who recovered the acute phase of the illness terminated by lysis six to ten days after the onset The majority of the patients who survived were left with severe mental and physical damage

The western type of the disease is much less severe the mortality varying from 15 to 25 per cent In fact serological surveys reveal many cases of subclinical infection

Diagnosis It must be emphasized that a diagnosis of encephalitis in man due to the virus of equine encephalomyelitis cannot be made on the basis of the clinical findings It may be confused with other types of acute infectious encephalitis such as polioencephalitis and St Louis encephalitis An increase in the incidence of encephalitis in man in an area where an epidemic of the disease is in progress in horses and mules should lead one strongly to suspect the equine type of the disease Virus was not isolated from any of the Massachusetts cases by inoculation of animals with blood or cerebrospinal fluid

A diagnosis can eventually be established in the majority of cases by certain biological tests The most important of these is the isolation of the virus from the brain tissue

creased pressure is sterile and may contain an increased number of cells which are usually mononuclear elements the amount of sugar is within normal limits

Diagnosis The clinical picture of postinfection encephalitis is at times not unlike that caused by certain known viruses for example St Louis encephalitis virus Consequently it is important to remember that not all cases of encephalitis occurring in the wake of infectious diseases are necessarily postinfection encephalitis In certain instances they undoubtedly represent other types for example some cases of encephalitis following antirabic vaccination are in reality rabies and some that occur after measles are of the hemorrhagic rather than the demyelinating type Often it is difficult and at times impossible by means of clinical observations alone to differentiate postinfection encephalitis from the other types In view of this fact a history of an encephalitis during convalescence from a virus malady usually results in a diagnosis of postinfection encephalitis As a rule such a diagnosis is correct but not always At present a definite diagnosis of postinfection encephalitis can be arrived at only by a careful examination of the brain and cord which should show a characteristic perivascular demyelination

Prognosis Ten to 50 per cent of the patients die the mortality rate is much higher in postvaccinal encephalitis (50 per cent) than it is in postmeasles encephalitis (10 per cent) the rate also varies from year to year being considerably lower now in postvaccinal encephalitis than it was in 1922–1925 The patients who recover usually do so completely sequelae occasionally occur and seem to be more frequent in cases developing after measles than in those following jennerian prophylaxis

Treatment The treatment is symptomatic Headache may be relieved by repeated lumbar punctures and the intravenous administration of hypertonic glucose solution

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Equine Encephalomyelitis

THE DISEASE IN HORSES

Equine encephalomyelitis has undoubtedly been present among horses and mules in this country for many years but was diagnosed as botulism forage poisoning and similar illnesses In 1931 it was proved to be caused by a filterable virus by Meyer Haring and Howitt during the course of their studies of an epidemic in the San Joaquin Valley in California Since then our knowledge of its extent epidemiology transmission and prevention has accumulated rapidly

In 1933 an epidemic occurred along the seacoast of Virginia and New Jersey and was shown by Ten Broeck and Merrill to be due to a virus immunologically distinct from that causing the disease in the West The eastern disease moreover is more severe than the western with a considerably higher mortality rate (about 90 per cent as compared to 25 to 30 per cent) The two diseases are referred to as the eastern and western types of equine encephalomyelitis

Epidemiology The first important clue to the mechanism of spread of epidemics was provided by Kelser s experiments in which he demonstrated that the virus could be transmitted by the mosquito *Aedes aegypti* Subsequently Kelser as well as other investigators showed that other mosquitoes including *A sollicitans A cantator A vexans A taeniorhynchus A dorsalis A nigromaculis* and *A albopictus* may transmit the virus It is of interest that the *Anopheles* mosquitoes fail to transmit the virus Recent experiments have demonstrated transmission of the virus by *Culex tarsalis* The mosquito transmission of the virus accounts for the spread of the disease in a particular area however it does not explain the sudden appearance of the malady in widely separated areas

Giltner and Shahan showed that pigeons were susceptible to infection after intracerebral inoculation of the virus and suggested that birds may play a role in the epizootiology of the disease Other investigators demonstrated that other species of birds are also susceptible During the course of the 1938 epidemic in Massachusetts Tyzzer Sellards and Bennett isolated the virus from pheasants dying in their natural state and Fothergill and Dingle isolated the

VIRAL DISEASES (PRESUMPTIVE)

Epidemic Hemorrhagic Fever

(Manchurian Fever)

Definition Epidemic hemorrhagic fever is an acute disease of unknown etiology which occurs during the spring and fall in northeastern Asia It is characterized by fever prostration vomiting proteinuria hemorrhagic manifestations shock and renal failure

History Beginning in 1951 seasonal outbreaks of a disease previously unknown to Western medicine occurred among the UN troops in Korea It was soon learned that the Japanese had encountered an identical clinical entity in eastern Manchuria which they named epidemic hemorrhagic fever This disease was apparently first described in Far Eastern Siberia under the name hemorrhagic nephrosonephritis by the Russians in the mid 1930 s

Etiology Russian investigators reproduced the disease in human volunteers by the parenteral injection of serum or urine obtained prior to the fifth day of illness from patients with the naturally occurring disease They further found that the disease agent was filterable through a Berkefeld filter (grade N) that the incubation period was usually twelve to sixteen days and that a single attack conferred immunity Extensive efforts to grow the causative agent on media and tissue cultures were failures as were efforts to establish the disease in a variety of lower animal hosts

Epidemiology and Mode of Transmission Hemorrhagic fever has been contracted only in northeastern Asia including Korea north of Seoul and perhaps in central Russia Sporadic cases occur throughout the year but large outbreaks in the late spring and fall account for the majority of attacks All ages sexes and races are susceptible The disease occurs only in rural areas and most cases occur as isolated events widely separated in time and place even during epidemics Person to person transmission does not occur Inability to isolate the causative agent has precluded definitive demonstration of the mode of transmission of epidemic hemorrhagic fever However its epidemiology is reminiscent of that of scrub typhus and careful studies strongly incriminate one or more species of trombiculid mites which infest certain field rodents

Morbid Anatomy Profound protein rich retroperitoneal edema is characteristic of early deaths in shock but not of later deaths Certain viscera are also edematous although dehydration of most regions is the rule The kidneys are swollen and exhibit extreme congestion sharply localized to the medulla while the right atrium appears hemorrhagic and the anterior pituitary exhibits congestion or hemorrhagic necrosis Similar congestion or hemorrhage may occur in the stomach adrenals lungs and central nervous system These areas derive their appearance from extremely dilated and congested small blood vessels especially in the renal medulla Petechial hemorrhages may occur in the skin heart adrenals and brain

Clinical Course and Pathological Physiology The clinical and laboratory manifestations of hemorrhagic fever make up a confusing array of problems that occur in rapid sequence with considerable overlapping and variation in severity However most patients follow a fairly typical course which is conveniently considered in relation to several phases The course of important clinical and laboratory features of a moderately severe case is shown in Figures 13 and 14 Although all patients exhibit proteinuria and many have petechiae and some degree of hemoconcentration hypotension and renal failure consequences such as shock serious hemorrhages and fluid and electrolyte imbalances occur in no more than 20 per cent

The febrile phase lasts three to eight days and is characterized by fever malaise a flush of the face and neck injection of the eyes and palate and other nonspecific features Evidence of widespread vascular dysfunction appears at this time Toward the end of the febrile pnase petechiae occur blood platelets decrease the hematocrit begins to increase and faint traces of protein appear in the urine

The hypotensive phase develops suddenly during defervescence and generally lasts one to three days Despite shock which

of acute fatal cases obtained at necropsy It is advisable to take small portions of brain tissue from various regions in the brain and brain stem The tissue is emulsified in physiological salt solution and inoculated intracerebrally into white Swiss mice or guinea pigs If virus is recovered it can be identified by immunological tests (protective tests in actively immunized animals or by serum neutralization tests) If it is impossible to inoculate animals immediately brain tissues can be preserved in the icebox in a mixture of 50 per cent neutral glycerin in buffered Tyrode solution It is important to preserve such material in a buffered mixture since the virus is inactivated rapidly by the developing cadaveric acidity Histological examination is of course of great value in diagnosis

In cases with a prolonged illness and in convalescent patients a diagnosis may be made by neutralization tests with patients serum Neutralizing antibodies appear seven to ten days after the onset of the illness

Treatment There is no specific therapy for this disease Treatment is entirely symptomatic consisting in the administration of sedatives for the control of convulsions administration of fluids parenterally and food by gavage during the period of coma

Prevention of the disease in man if an epidemic occurs should consist largely in sanitary measures Houses and particularly sleeping quarters should be screened against mosquitoes and children should not be allowed outside after sundown A vaccine has been used in persons under unusual risk such as laboratory workers The infrequency of the disease in the latter does not justify large scale vaccination

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Infectious and Serum Hepatitis

See under Diseases of the Liver

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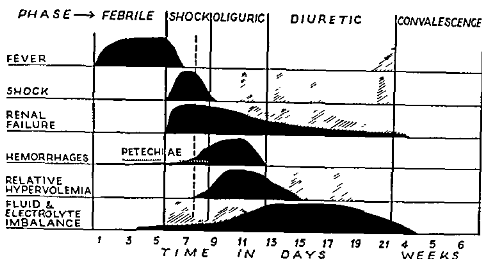


FIG 13 Hemorrhagic fever abnormal physiology

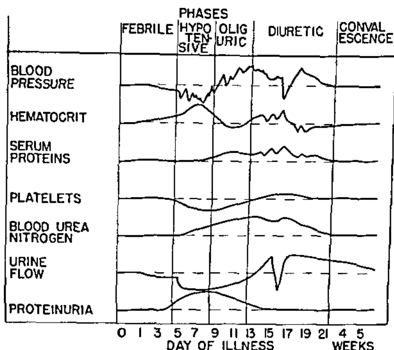


FIG 14 *Severe hemorrhagic fever course of certain laboratory findings*

accounts for a third of all deaths the extremities may remain warm and arteriolar dysfunction may contribute to the hypotension The dominant feature however is a reduction in blood volume due to loss of plasma from the vascular system as evidenced by a rapid increase in hematocrit to as high as 70 per cent and to trapping of erythrocytes in dilated capillaries Heavy proteinuria oliguria acute renal failure and hemorrhages of capillary origin associated with thrombocytopenia are prominent clinical features whether or not hypotension develops Nausea and vomiting are common while backache and abdominal discomfort result from localized edemas The leukocytes which earlier were normal or reduced now show a leukemoid reaction

The oliguric phase begins as the hematocrit decreases and the sequestered plasma returns to the vascular system It usually lasts for three to five days Deaths in this phase are due to pulmonary edema electrolyte abnormalities and shock secondary to dehydration or pulmonary complications This phase is *one of increasing* renal failure and nitrogen retention continued vomiting and dehydration Hyperkalemia is common *Despite improvement in many of the earlier* symptoms increasing confusion and extreme restlessness are common as is hypertension Some patients exhibit a *hyper*

volemic syndrome which may respond to phlebotomy Hemorrhages into the skin sclerae gastrointestinal tract lungs and renal pelvis continue but rarely are large in amount and generally decrease toward the end of the oliguric phase

The diuretic phase which may last for days or weeks usually initiates clinical recovery and rapid improvement in renal function However a diuresis of 3 to 8 liters daily represents a hazard to patients who are already extremely dehydrated and who have had limited caloric intake for seven to ten days These patients exhibit a brittle fluid volume homeostasis and may fluctuate rapidly between shock on the one hand and hypertension and pulmonary edema on the other depending on the state of the fluid balance Serious potassium deficiency is not uncommon while hyper natremia can be troublesome Deaths in this phase account for a third of the total and are usually due to shock secondary to dehydration and to pulmonary complica tions including bacterial infections The diuresis characteristic of this phase does not represent mobilization of edema fluid but is the result of residual renal tubular damage

Convalescence requires three to twelve weeks and is characterized by gradual re turn of appetite strength and urinary con centrating ability to normal

Diagnosis In the absence of any specific test the diagnosis must be made on clinical evidence and should be suspected when an acute febrile illness associated with the characteristic flush and petechiae occurs in a subject who has been in an endemic area The subsequent developments such as hypo tension or shock increased hematocrit thrombocytopenia oliguria and renal fail ure assist in establishing the diagnosis but 3 to 4 plus proteinuria developing near the time of defervescence is the single most useful diagnostic sign

Prognosis The case fatality rate among U S Armed Forces once techniques for prompt diagnosis and early adequate treat ment were developed has been 5 per cent or less No single finding is of great prog nostic value in individual patients How ever prolonged high fever protracted or recurrent shock and persistent hemocon centration are all ominous features With rare exceptions survivors who have not had central nervous system hemorrhages make apparently complete recoveries

Treatment Since antimicrobial drugs convalescent serum hormones and other agents are entirely ineffective the manage ment of hemorrhagic fever must be suppor tive and based on an understanding of its physiological and biochemical characteris tics and on frequent clinical observations Adequate sedation with barbiturates or opi ates is frequently required for restlessness Contrary to the practice in other febrile diseases fluid intake must be limited since any excess will simply leak out of damaged capillaries and increase edema and symp toms When intravenous fluid is required it usually should be 10 per cent dextrose in water and must be given very slowly If shock fails to respond to simple measures such as shock blocks then concentrated (salt poor) human serum albumin to re store plasma volume and continuous intra venous infusion of pressor drugs (pref erably Arterenol) may be required Doses of the latter must be based on the response of the shock blood pressure and hemato crit Occasionally large doses of both al bumin and pressor drugs are required Treatment in the oliguric phase is that of acute renal failure with careful control of electrolytes and particular attention paid to hyperkalemia If oliguria persists for more than a few days 20 to 50 per cent dextrose in water (600 to 800 ml per day) may be given by continuous intravenous drip through a polyethylene catheter placed in a great vein Phlebotomy may be required for the fully developed hypervolemic syndrome The chief problem of the diuretic phase is one of careful matching of fluid and electro lyte intake against the brisk urinary output so as to avoid excessive dehydration and shock on the one hand and hypervolemia and pulmonary edema on the other Elec trolyte abnormalities are still a problem especially potassium deficiency

Prevention Preventive measures are based on the assumption that the disease is transmitted by an arthropod parasite of a rodent Control of the rodent population and individual measures such as dipping all clothing in miticide solution and use of insect repellents have been used by the Armed Forces in Korea The effectiveness of such measures has not yet been established although each outbreak of hemorrhagic fever in Korea has been smaller than the preceding epidemic

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Infectious Mononucleosis

Definition Infectious mononucleosis is a disease of unknown etiology and of protean symptomatology occurring principally in the first three decades of life and characterized typically by lymphadenopathy lymphocytosis (largely due to abnormal lymphocytes) and an elevated titer of sheep cell agglutinins in the serum

History Emil Pfeiffer in 1889 is generally credited with having first called attention to the disease which he termed glandular fever West was the first to report the disease in the United States The *increase in the small mononuclear elements in the* blood was reported by Burns in 1909 Between 1909 and 1920 various reports were made of what appear to have been sporadic forms of the disease In 1920 the term infectious mononucleosis was proposed *by Sprunt and Evans who also called attention to* the presence of abnormal cells in the blood Downey and McKinlay made a detailed report of the hematological findings in 1923 Paul and Bunnell in 1932 were the first to call attention to the presence of *sheep cell agglutinins in the serum in this disorder*

Incidence Infectious mononucleosis is not limited to any one geographical location It *has been reported in America Europe* Egypt Australia China Japan and elsewhere It may occur in either the epidemic or the sporadic form although most reports *have dealt with the latter type The disease* may occur at any age cases having been reported at seven months and seventy years but the great preponderance of patients *with the disease is found between the* ages of ten and thirty five Until recently it has been thought that the incidence in Negroes was low However a number of *cases of the disease in Negroes have been* reported in the past few years Wechsler and his co workers found that forty nine Negroes or 8 7 per cent of the total number of patients in a large epidemic were affected

Etiology Infectious mononucleosis presumably represents either a single infection or a common host reaction pattern to several infections for it may occur as a localized epidemic as well as in the form of sporadic cases It is generally considered that a virus or filterable agent is responsible for the condition but as yet no definitive proof of this has been offered Transfer of the disease to monkeys by means of a filtrate of nasal washings has been reported but there has been failure to confirm this work During recent years a wide variety of inoculums have been used in sixty one individual attempts to transfer the disease to human volunteers Successful results have been claimed in only two instances Evans who is responsible for twenty one of the experiments in human beings had negative results as regards transmission of the disease in every instance He suggested that failure to transmit the disease might be due to extreme lability of the causative organism and/or to low individual susceptibility Whatever the answer may be the evidence at the present time does not justify any designation of the causative factor

Morbid Anatomy The morbid anatomy of infectious mononucleosis is much more clearly understood than previously as a result of postmortem studies on several *patients who succumbed to the disease* Gross changes are limited almost entirely to enlargement of the lymphoid tissue including the spleen Other gross features *include frequent enlargement of the liver* rare icterus and occasional skin lesions The histological lesions tend to be generalized and closely resemble those of some of *the viral diseases They consist mainly of* perivascular aggregates of normal and abnormal lymphocytes Most of the tissues with the exception of the bone marrow *have been shown to have these lesions* The lymphocytes are absent in the bone marrow sections whereas aspirated marrow specimens do contain them as a consequence of *admixture with peripheral blood* Recently granulomatous lesions have been demonstrated in the bone marrow The lymph nodes which contain large numbers of the *abnormal lymphocytes* show varying pictures from follicular hyperplasia to changes simulating those of a malignant lymphoma Lymphocytic infiltration of the capsule and trabeculae of the spleen occurs regularly The trabeculae are often dissolved by these infiltrations resulting in rupture of the spleen in rare instances Perivascular accumulation of the lymphocytes about the arteries of the trabeculae is to be expected Moreover subintimal accumulation of these cells in the veins of the spleen is constantly found Pneumonic exudate of either the round cell or neutrophilic types may occur Small myocardial infiltrates are found fre

quently In addition periportal round cell accumulation in the liver and various lesions of the nervous system in particular meningo-encephalitis are often encountered

Symptoms Infectious mononucleosis is protean in its manifestations The classic or so-called "typical" case may be described as follows

A young adult is typically affected probably five to fifteen days after exposure to the causative organism Malaise with or without sore throat but with fever and lymphatic enlargement—more typically of the posterior cervical nodes but frequently of all the nodes—characterizes the onset The fever is of no definite type but usually is not pronounced It lasts ordinarily for five to ten days but variations from absence to persistence for several weeks may occur The nodes which are moderate in size (usually not over 3 cm in diameter) discrete slightly indurated nonsuppurative and sometimes slightly tender generally return to normal size in three to four weeks Slight splenomegaly occurs in approximately one third of the cases and ordinarily recedes at the same time as the lymphadenopathy The duration of active clinical signs and or symptoms varies from a few days to a few weeks or more Leukopenia is common in the first week of the disease followed by moderate leukocytosis in the second and third weeks This leukocytosis is due to an increase in the number of lymphocytes many of which are abnormal In general the leukocyte picture returns to normal gradually within three to four weeks The sheep cell or heterophile agglutination test becomes positive usually within the first two weeks of the illness The thymol turbidity test is said to be positive in as high a percentage of cases as the sheep cell agglutination test Some of the other liver function tests have also shown abnormal findings Serological tests for syphilis may be positive in 3 to 10 per cent of the cases No other significant abnormal laboratory findings occur in the usual patient with this disease

Toxic symptoms such as headache malaise generalized aching anorexia and so forth are present in the acute phase in many instances Moreover exudative pharyngitis tonsillitis and gingivitis with or without Vincent s organism occur in an appreciable percentage of the cases

Some of the many variations which may be found in this disease are worthy of special comment

Latent Forms The disease occurs in an appreciable number of persons in the absence of signs or symptoms the diagnosis being made by means of changes in the leukocyte picture and/or serological tests

Cutaneous Eruption Skin eruptions of one type or another may occur Wechsler and his associates reported dermatological lesions in 16 per cent of their patients but the incidence in other reports has varied from 4 to 100 per cent The most common skin rashes are of the macular and/or maculopapular types Other types such as morbilliform polymorphous nodular vesicular urticarial and hemorrhagic are found at times

Abdominal Types Jaundice with or without hepatomegaly may occur in a small number of patients being found in 6 per cent (thirty four cases) of those composing the epidemic studied by Wechsler Liver biopsies abnormal liver function tests and autopsy findings have indicated that hepatitis rather than obstruction of the common duct by enlarged lymph nodes is responsible for the jaundice In very rare instances the hepatitis may be extreme It must be emphasized however that there is no certain way to distinguish between hepatitis as a complication of mononucleosis and viral hepatitis Hence in the absence of serological evidence of infectious mononucleosis it is advisable to manage the illness as if serum or infectious hepatitis were present

Abdominal pain secondary to enlarged mesenteric nodes is not uncommon Rarely appendiceal involvement and rupture of the spleen may occur Thirteen cases of rupture of the spleen with five deaths have been reported

Cardiac Involvement Focal myocarditis and electrocardiographic changes such as abnormal T waves and prolonged P R intervals are common However clinical symptoms referable to the heart are conspicuously absent

Pulmonary Involvement Clinical evidence of pulmonary involvement is rare Wechsler and his colleagues have reported that 2 5 per cent of their cases showed pulmonary lesions similar to those of atypical pneumonia Whether the pulmonary changes in these cases were due to infectious mononucleosis or to some secondary complicating infection is not established

Neurological Involvement Symptoms indicative of involvement of the cerebral meninges the brain the cranial nerves the peripheral nerves the spinal roots and the spinal cord have been reported Typical cases of the Guillain Barre syndrome have

occurred in two of these deaths resulted Also cases of encephalomyelitis with a symptomatology suggesting poliomyelitis have been reported Pleocytosis and changes in the protein content of the cerebrospinal fluid may occur Seven patients with central nervous *system involvement are known to* have died as the result of neurological complications

Hematological Abnormalities Granulocytopenic leukopenia at the onset followed by lymphocytic leukocytosis constitutes the principal abnormality in the blood In some instances polymorphonuclear leukocytosis precedes the lymphocytic leukocytosis and the granulocytic leukopenia The leukopenia is usually supplanted by leukocytosis during the second week of illness owing to an increase in the number of lymphocytes many of which are abnormal Downey s description of the three types of abnormal lymphocytes which may occur still remains one of the best His *Type I* cell is characterized by heavy *staining* irregular or bean shaped nuclei without nucleoli and with dark blue foamy cytoplasm His *Type II cell is characterized by relatively large* amounts of light blue cytoplasm and a relatively normal appearing eccentrically placed nucleus His *Type III* cell occurs much less often than either *Type I* or *Type II* and is distinguished by its resemblance to malignant or leukemic cells The lymphocytosis is of varying degrees and is both relative and absolute The percentage of lymphocytes varies widely at times being above 90 Further the actual percentage of abnormal lymphocytes varies greatly from patient to patient These abnormal cells are *in no sense specific* being found in a variety of clinical disorders particularly some of the viral infections Epidemic or infectious hepatitis at times has a leukocyte picture indistinguishable from that found in infectious mononucleosis A similar but less marked blood picture may be found at times in a number of acute illnesses of viral origin Most of the lymphocytes are approximately the size of small or intermediate lymphocytes but there are usually a few cells much larger and with nuclei showing nucleoli

In most patients the leukocyte picture is the only blood change of any significance However a few cases with anemia and/or thrombocytopenia have been reported Also hemolytic anemia may occur rarely Agranulocytosis has been noted in only one instance An increased erythrocyte sedimentation rate is found but of course is in no sense specific

Serological Findings The sheep cell or heterophile agglutination test constitutes one of the most important diagnostic procedures in this *disease* Paul and Bunnell were the first to call attention to this fact They assumed that the heterophile antibody *of infectious mononucleosis was of the* Forssman type but Bailey and Raffel and Stuart showed later that this antibody could be distinguished from that of serum sickness and from that of normal serum Thus there may be at least three types of agglutinins for sheep cells in the serum of human beings The agglutinins associated with serum sickness have been said to be completely adsorbed by either guinea pig kidney or beef erythrocytes those associated with normal serum to be almost completely adsorbed by guinea pig kidney but not by beef erythrocytes and those associated with infectious mononucleosis to be completely adsorbed by beef erythrocytes but not significantly by guinea pig cells *However Dempster has called* attention recently to the fact that there are distinct exceptions even to these latter assumptions

There has been considerable argument as to what constitutes a significant titer in infectious mononucleosis This probably varies from laboratory *to laboratory* depending upon the technique used Paul has suggested the following ranges for titers 1 10 to 1 40 negative *1 80 to 1 160* suspicious above 1 160 positive A rising titer is the best criterion in the early stages of the disease The differential adsorption tests are of distinct advantage particularly when the titer is in the lower ranges In rare instances Hodgkin s disease and leukemia may have very high titers which are completely abolished by adsorption with guinea pig kidney Usually adsorption with guinea pig kidney is satisfactory but in some instances adsorption by both guinea pig kidney and beef erythrocytes is needed to clarify the diagnosis The exact incidence of the positive sheep cell agglutination test in infectious mononucleosis is not established Certainly all cases do not show the positive test In Paul s series the test was positive for 20 to 40 per cent of the cases in the first week for 60 per cent of the cases in the second week and for considerably fewer in the fourth week *In* Dempster s series 66 per cent of the cases of infectious mononucleosis gave positive agglutinin adsorption reactions *Hemolysins* for ox cells are often greatly elevated in infectious mononucleosis and appear to retain a diagnostic *titer for a longer period* than do sheep cell agglutinins Titration of

these hemolysins may therefore have particular value at a time when the agglutinin titer may be suspected to have declined

As previously indicated the serological tests for syphilis are falsely positive for a small number of these patients possibly 3 to 10 per cent Moreover *cold agglutinins* in significant titer and abnormal liver function tests have been reported

Diagnosis The diagnosis of infectious mononucleosis is not difficult in the typical case with lymphadenopathy splenomegaly lymphocytosis and positive sheep cell agglutination All of these findings may be absent in certain stages of the disease however and one or more of them may be absent throughout the illness Streptococcal sore throat Vincent s angina and diphtheria may be confused with the oropharyngeal lesions Infectious hepatitis and homologous serum jaundice may be mistaken for this disease and vice versa since the leukocyte picture may be identical in these disorders Typhoid fever and undulant fever may be confused with the disease at times when leukopenia is present The skin lesions may lead to confusion with typhus fever rubella secondary syphilis and scarlet fever The neurological involvement may raise the question of a large number of neurological disorders such as lymphocytic choriomeningitis encephalitis Guillain Barré disease and poliomyelitis Leukemia idiopathic thrombocytopenic purpura and infectious lymphocytosis may be simulated at times Infectious lymphocytosis is differentiated by hyperleukocytosis negative sheep cell agglutination test and the absence of atypical lymphocytes

Prognosis In general the prognosis of infectious mononucleosis may be considered good Most of those affected recover within three to six weeks without sequelae However severe complications such as hepatitis thrombocytopenia myocarditis spontaneous rupture of the spleen and involvement of the central and/or peripheral nervous system may occur Several instances of fatal outcome from rupture of the spleen involvement of the nervous system and myocarditis have been recorded In rare instances the spleen and/or lymph nodes may remain enlarged for long periods of time Neurological symptoms may persist for varying intervals Neurological complications and rupture of the spleen account for most of the deaths (12 out of 16) from this disorder Recurrences and relapses have been reported but the writer s experience is in conformity with that of Contratto to the effect that they are generally absent in patients who have actually shown recovery

Treatment There is no specific treatment for infectious mononucleosis Sulfonamides penicillin chloramphenicol and the tetracyclines have been tried without evidence of benefit Rest is indicated in the presence of acute symptoms It is probably wise to limit activities considerably in any known case even when fever and acute symptoms are *absent because of the danger of rupture of* the spleen When jaundice is present a high carbohydrate and protein diet in addition to limitation of activities is indicated Palliative measures of various types depending upon the symptomatology in individual cases are indicated In severely ill patients a prompt remission can usually be obtained by the use of corticotropin or cortisone but the advantages and disadvantages of such treatment have not yet been defined

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Cat Scratch Disease*

(Cat Scratch Fever Sterile Regional Lymphadenitis Benign Lymphoreticulosis of Inoculation)

Definition Cat scratch disease is a benign subacute regional lymphadenitis which may proceed to sterile suppuration or subside spontaneously An indolent primary skin lesion at the site of a cat scratch precedes the adenitis

* Appreciation is expressed to Dr Frank G MacMurray for his assistance in the preparation of this section

History About 1932 Foshay in Cincinnati differentiated the disease from tularemia and Debre in Paris independently recognized it as a specific entity Hanger and Rose devised a specific intradermal test in 1945

Incidence Since the description of cat scratch disease by Debre in 1950 hundreds of cases have been recognized throughout the world It is a common disease and wherever physicians become informed of its manifestations many cases are found

Epidemiology Most victims have cat contacts the majority being scratched and a few bitten Occasionally inoculation follows the prick of a thorn or splinter Household epidemics center about the family cat Suspected cats appear healthy and presumably transmit the disease passively Children are affected more frequently than adults

Etiology The causative agent has not been isolated The disease has been transmitted to monkeys and to one human by intracutaneous inoculation of infected lymph node suspension Granular corpuscles found in cells of nodes are considered by some to be a visible form of the "virus and by others to be nonspecific A minority of patients have a low titer of complement fixing antibodies to lygranum complement fixing (CF) antigen The reaction however is also found in others especially among older controls not affected with the disease and with no history of an attack *Complement fixing reactions to* lygranum CF is thus without diagnostic value in the individual case and affords no convincing evidence that the disease belongs to the psittacosis lympogranuloma *group of diseases*

Pathology Histologically the lymph nodes have shown reticuloendothelial hyperplasia and later focal granulomas with necrotic centers surrounded by epithelioid cells Langhans giant cells are common The process frequently involves the pericapsular connective tissue

Clinical Manifestations A few days following a cat scratch or other skin injury about half the patients develop an indolent primary skin lesion This appears as a persistent infected scabbed ulcer or scratch or a papule surmounted by a vesicle or pustule About one to three weeks later the regional lymph nodes become remarkably enlarged and fever and symptoms of infection usually develop The nodes may be elastic movable and virtually insensitive or fixed red and tender They may recede spontaneously in weeks to months or suppurate with the development of sterile pus Lymphangitis does not occur The epitrochlear axillary and inguinale femoral forms are unilateral the cervical form is frequently bilateral Enlarged nodes may occur in unusual sites as under the ed e of the pectoral or trapezius muscles Infected thyroglossal cyst may be simulated

Rarely the eye is the site of inoculation causing *Parinaud s oculoglandular syndrome* (unilateral conjunctivitis with enlargement of the homolateral preauricular lymph node) Encephalitis occasionally complicates the disease recovery occurring without residuals Macular or papular rashes and erythema nodosum are occasionally seen

Laboratory Findings *Intradermal Test* Aspirated pus is diluted 1 5 with isotonic sodium chloride solution and heated to 60 C for one hour on two consecutive days When proved sterile 0 1 ml is injected intracutaneously At forty-eight hours a positive reaction is indicated by a papule 0 5 to 1 0 cm in diameter or an area of erythema 1 0 to 6 0 cm in diameter or both A positive reaction is indicative of past or present infection Negative reactions however have been obtained in a few patients who had illnesses clinically and often pathologically suggestive of cat scratch disease

The leukocyte count is usually normal The erythrocyte sedimentation rate is often rapid Cultures of pus or removed nodes are sterile

Diagnosis Cat scratch disease may simulate a wide variety of lymph node diseases such as tularemia infectious mononucleosis lymphosarcoma Hodgkin s disease *tuberculous adenitis pyogenic adenitis* subcutaneous abscesses lymphogranuloma venereum and both benign and malignant tumors Appropriate examinations to exclude other diseases and the intradermal test with cat scratch disease antigen will lead to the proper diagnosis In the presence of a typical clinical history pathological findings consistent with this disease and a positive intradermal test an unequivocal diagnosis can be made Whenever there is doubt as to the etiology of a lymph node disease an intradermal test with cat scratch *antigen may avoid the necessity of* biopsy and release the patient and physician from the fear of some more serious ailment

Prognosis This is a benign self limited disease which may last from two weeks to *two years*

Treatment Chloramphenicol or the tetracyclines may shorten the course of the disease and prevent suppuration Suppura

tive nodes should be aspirated Excision or drainage may be necessary

WORTH B DANIELS

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Acute Infectious Nonbacterial Gastroenteritis

Definition So-called nonbacterial gastroenteritis or viral enteritis is an acute self limited infection of diverse etiology The afebrile type is characterized by watery diarrhea abdominal cramps nausea and vomiting An unrelated febrile type is non diarrheal Both are apparently due to viruses as yet not cultivated Febrile diarrheal disease *especially in children* may be caused by certain enteroviruses

Incidence and Epidemiology The disease is worldwide The epidemiological unit seems to be the family in which nonbacterial gastroenteritis may rank second to common respiratory disease in frequency Both sexes and all ages are affected The mode of transmission is fecal-oral The afebrile disease which is highly communicable occurs in large epidemics more frequently in the cold months and also sporadically The incubation period ranges from one to five days averaging three days The febrile type has an incubation period of one or two days and is less contagious than the afebrile form The epidemiology of the diarrheas due to enteroviruses is complicated by the high carrier rate in healthy children

Etiology and Pathology The causative agents of the afebrile and febrile types have not been propagated in the laboratory but human volunteers were infected when fed bacteria free fecal supernates Volunteers were actively immune to one strain of the afebrile agent for a year but there may be antigenic variants The afebrile agent passes through ultrafilters Neither disease causes fatalities The afebrile type is a rare terminal complication in patients ill of other disease especially the aged The pathological findings consisting of intestinal hyperemia and occasional ulceration can be attributed to hypermotility The enteroviruses which induce diarrheal disease are usually members of the ECHO group but polioviruses or Coxsackie viruses sometimes cause gastroenteric symptoms and signs

Symptoms The onset of the afebrile type is often abrupt with profuse watery diarrhea anorexia nausea and vomiting occurring singly or in combination Usually there are hyperperistaltic abdominal cramps often preceding a watery stool Dizziness mild headache and malaise are frequent complaints When there is fever it is low and related to mild or moderate dehydration The abdomen is relaxed and the colon distended with gas may be palpated Borborygmi are heard and felt Respiratory symptoms and signs are often conspicuously absent if present they may be adventitious The blood count and other clinical laboratory values are normal and the feces seldom contain blood pus or mucus The acute illness lasts only a day or so although stools may be loose for a week

The febrile type differs *in that there is* no watery diarrhea some patients are constipated Abdominal pain tends to be persistent is frequently intense and is often accompanied by moderate fever headache and malaise Patients recover within two days

Children suffering from diarrhea due to an enterovirus may exhibit fever vomiting and abdominal pain Blood and mucus may occur in the stools The disease is usually self limited

Diagnosis and Treatment Culture and microscopy of the feces are important in differentiation of nonbacterial gastroenteritis from salmonellosis shigellosis or amebiasis particularly in epidemics of the afebrile type Absence of fever or leukocytosis may be helpful Food poisoning can often be excluded by the distribution and timing of new cases which may continue to appear for over a week Febrile nonbacterial gastroenteritis can resemble early

acute surgical conditions but it fails to progress and is soon over A cytopathogenic agent can be isolated in tissue culture from feces of patients with enterovirus infection The virus carried may be unrelated to illness so isolation of an enterovirus from the stool is of little diagnostic value unless accompanied by demonstration of an increase in serum antibody

Treatment is rarely needed and consists only of fluid replacement

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RICKETTSIAL DISEASES

Introduction

The rickettsial diseases of man are caused by microorganisms which are classified as a family (*Rickettsiaceae*) between the bacteria and the viruses because they have characteristics in common with both These microorganisms were named "rickettsiae to honor the observation made by Dr H T Ricketts in his studies of Rocky Mountain spotted fever and epidemic typhus fever In 1910 while investigating the etiology of typhus Ricketts contracted this disease and died Several species of rickettsiae are now recognized as pathogenic for man Their individual characteristics are described in the sections dealing with the various human infections which they induce In general the rickettsiae have four common features (*a*) they are pleomorphic cocco bacillary forms readily visible in the ordinary light microscope (*b*) they multiply only within certain cells of susceptible animals (*c*) they occur in various arthropods in nature and (*d*) they cause acute febrile self limited illnesses in man most of which are accompanied by a skin rash

The principal rickettsial diseases are divided into groups as indicated in the accompanying table

The distinctive clinical course typical of each disease has been the primary basis for the classification shown in the table There are also differences between the usual mode of transmission The specific immunological properties of the rickettsiae and their differences biologically as revealed in laboratory studies are more valuable and more reliable in the classification of the rickettsial diseases than either the clinical features or the arthropod vectors After recovery from any one of the individual diseases shown in the table the blood serum of man and certain animals has highly specific antibodies in complement fixation or rickettsial agglutination tests These serological procedures not only indicate the main group to which a particular disease belongs but also distinguish between the members of the same group in certain instances

Before specific serological techniques with rickettsial antigens were fully developed the Weil Felix test was the only simple procedure available for laboratory differentiation of the rickettsial diseases The Weil Felix test is described in the section on the diagnosis of typhus fever The basis of the reaction is believed to be a fortuitous occurrence of a common antigenic component between some rickettsiae and certain strains of the bacillus *Proteus vulgaris* It should be emphasized that there is no etiological relationship between rickettsial diseases and the strains of *Proteus vulgaris* used in the Weil Felix test Although this test is immensely helpful in epidemics of classic typhus and in the investigation of scrub typhus it has important limitations and no longer serves as a primary criterion in the identification and classification of rickettsial diseases

The immunity produced by the rickettsial diseases is usually of long duration The members of one group confer either partial or complete immunity to the other diseases of the same group but no cross immunity occurs between the different groups Unfortunately there are several instances of fatal infections among laboratory workers which emphasize this point for example tsutsugamushi disease has taken the lives of persons who had previously experienced epidemic typhus

The rickettsial diseases include one of the notorious diseases of medical history epidemic typhus fever which has been a scourge of mankind for more than four centuries as well as two "new" diseases not recognized clinically before 1935 (Q fever) and 1946 (rickettsialpox) Some of the rickettsial diseases such as murine typhus are world wide in distribution others are known only in certain areas for example rickettsialpox It is of considerable interest that microorganisms indistinguishable in appearance from pathogenic rickettsiae are found as harmless symbionts in many different arthropods Students of the rickettsiae particularly Wolbach and Zinsser have stressed the possible occurrence of rickettsial diseases whenever man rodents and ectroparasites common to both are

Rickettsial Diseases of Man

GROUP	PRINCIPAL DISEASES	SYNONYMS	ETIOLOGIC AGENT	USUAL MODE OF TRANSMISSION TO MAN	USUAL OCCURRENCE
Typhus	Epidemic typhus	Classic historic human European typhus[1]	*Rickettsia prowazeki*	Human body louse	Winter and spring in cold climates over most of world
	Brill Zinsser disease	Brill s disease recrudescent typhus	*Rickettsia prowazeki*	See text[3]	U S A Europe probably world wide[3]
	Murine typhus	Endemic typhus urban or shop typhus of Malaya	*Rickettsia mooseri*[4]	Rat flea[5]	World wide
Rocky Mountain spotted fever[6]	Rocky Mountain spotted fever	Spotted fever tick fever tick typhus etc	*Dermacentroxenus rickettsi*[7]	Ticks[8]	North and South America
	Fievre boutonneuse	Button fever Mediterranean fever	*Dermacentroxenus conori*[9]	Ticks[10]	Mediterranean countries and North Africa
	South African tick bite fever		*Dermacentroxenus pijperi*	Ticks[11]	South Africa
	Rickettsialpox	Kew Gardens fever	*Rickettsia akari*[1]	Mites[13]	Northeastern U S A [3] Korea
Tsutsugamushi disease	Scrub typhus	Mite borne typhus Japanese river fever tropical typhus ruraltyphus Sumatran mite fever etc	*Rickettsia tsutsugamushi (orientalis)*	Mites[14]	Korea Japan China Formosa India Burma Ceylon Indonesia the Philippines and Australia
Q fever	Q fever	Nine mile fever Australian Q fever Balkan grippe	*Coxiella burnetii*[15]	Probably air borne route occasionally ticks possibly milk[3]	Australia, U S A Panama Europe North Africa (probably world wide)

[1] Jail fever war fever camp fever *Fleckfieber* (German) *typhus exanthematique* (French) *tifus exantematico* (Spanish) *dermotypho* (Italian)
Pediculus humanus corporis
[3] See text for further explanation
[4] Bergey s Manual classification *Rickettsia typhi*
[5] *Xenopsylla cheopsis*
[6] In addition to the diseases listed there are others which probably belong in this group such as North Queensland tick typhus tick borne rickettsioses of India and Kenya
[7] Bergey s Manual classification *Rickettsia rickettsii*
[8] *Dermacentor andersoni D variabilis Amblyomma americanum*
[9] Bergey s Manual classification *Rickettsia conorii*
[10] *Rhipicephalus sanguineus*
[11] *Amblyomma hebraeum Haemaphysalis leachi*
[1] In author s opinion name *Dermacentroxenus akari* would be preferable
[13] *Allodermanyssus sanguineus*
[14] *Trombicula akamushi T deliensis*
[15] *Rickettsia diaporica* was the name first used for the American variety of Q fever rickettsiae

closely associated Indeed the list of rickettsial diseases in the accompanying table indicates only the principal human rickettsial infections For example a disease called North Queensland tick typhus has been reported from Australia (1947) which probably is a member of the Rocky Mountain spotted fever group but it has not been completely characterized trench fever or Wolhynian fever is reputed to be a rickettsial disease of man transmitted by the human body louse from man to man yet

its position in respect to the other rick ettsiae has not been established

One final point of general interest in re spect to the rickettsial diseases should be mentioned Recent developments have added enormously to the means for com bating these infections Satisfactory vac cines have been prepared on a large scale against some of the rickettsial diseases The methods for rapid mass delousing with the insecticide DDT have demon strated how effectively the once dread epidemics of typhus can be sharply ar rested Finally several of the new anti microbial drugs if used early in the illness have a dramatic effect on the clinical course of the rickettsial diseases These advances greatly reduce the severity and the magni tude of the problems associated with the rickettsial diseases

The Typhus Group

Definition Typhus fever is an acute in fectious disease characterized by severe headache sustained high fever generalized macular or maculopapular rash and ter mination by rapid lysis in approximately two weeks

Three diseases compose the typhus group epidemic louse borne typhus fever Brill Zinsser disease and murine flea borne typhus fever Clinically and pathologically these three illnesses are nearly identical differences occurring only in the intensity of the symptoms and signs the severity of the course and the case fatality rate Epi demiologically and historically however the three members of the typhus group are so different that they are described in separate sections

EPIDEMIC LOUSE BORNE TYPHUS FEVER

(*Classic Historic Human European Typhus Jail Fever War Fever Camp Fever Flecl fieber* [*German*] *Typhus Exanthematique* [*French*] *Tifus Exantemático Tabardillo* [*Spanish*] *Dermotypho* [*Italian*])

History It is probable that typhus fever has af flicted mankind since ancient times but the account of Fracastorius in 1546 is the earliest medical record which describes typhus fever with sufficient accu racy to permit its definite identification The word *typhus* is derived from the G eek *typhos* meaning smoky or hazy Although the term had been used by Hippocrates to describe a confused state of intellect with a tendency to stupor it was not applied to cases which were clearly typhus fever itself until 1760 Despite the work of Fracastorius typhoid and typhus fevers were usually regarded as one entity by physicians until 1837 when Gerhard in Philadel phia clearly differentiated the two disorders on the basis of important differences clinically and patho logically Even today however confusion in term inology persists in those parts of Europe where *typhoid* fever is called typhus abdominalis

Typhus fever has had a major role in the history of the past four centuries It followed in the wake of wars famines and human misfortunes of all kinds It has often had a more decisive effect on military campaigns than the actual battles them selves a subject admirably treated by Zinsser in his book *Rats Lice and History* The typhus epidemics in eastern Europe and Russia between 1918 and 1922 are estimated to have caused 30 000 000 cases and at least 3 000 000 deaths It is worthy of com ment that the ravages of typhus have character istically been even greater among medical personnel than among the general population In the 1915 epidemic in Serbia nearly all of the 400 doctors in that country contracted tyhus and 126 died Thus typhus has established its reputation as one of the major epidemic diseases

Etiology and Transmission In 1916 da Rocha Lima showed that typhus was caused by the microorganism which he named *Ricl ettsia prowazel i* This microorganism has been found in nature only in man and the human louse *Pediculus humanus* Sev eral other species can be experimentally infected with *R prowazeki*—for example monkeys guinea pigs cotton rats gerbilles mice fleas and developing chick embryos The numerous instances of typhus fever among laboratory investigators working with experimental typhus infection clearly indicate the validity of the conclusions reached by Wolbach Todd and Palfrey in their classic monograph on the etiology of typhus fever (1922)

The microorganism is present in the blood of typhus patients during the febrile period particularly in the first few days of the illness Human lice feeding on the patients ingest the typhus rickettsiae which then multiply within the lining cells of the intestinal tract of the louse The cells be come greatly distended with masses of *R prowazeki* and may burst into the lumen of the gut whereupon the microorganisms invade other lining cells or pass out of the louse in the feces After several days the louse gut becomes occluded by the dis tended typhus infected cells and the louse dies of intestinal obstruction Chronic in fection of lice with typhus rickettsiae has not been demonstrated The microorgan isms do not pass to new generations via the louse egg

When the louse feeds it makes a small puncture in the skin secretions of the louse introduced during the act of feeding irri tate the skin causing the bitten person to scratch It is characteristic of the louse that it defecates as it feeds so that con ditions are ideal for the rubbing of typhus

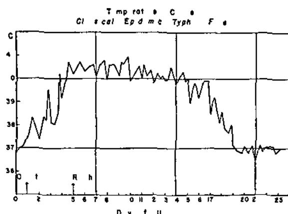


Fig 15 Temperature curve in a case of classic epidemic tyhus (Courtesy of Dr T M Rivers Viral and Rickettsial Infections of Man J B Lippincott Company)

rickettsiae into the skin punctures Two factors explain the movement of typhus infected lice from the persons whose blood has infected them to normal persons the insects tend to leave a patient who has a high fever if other hosts are available and if the host dies of typhus the body becomes cold and the lice promptly crawl away in search of another host These facts probably account for much of the transmission of typhus during epidemics

Another important way in which transmission may occur is by contact with infected louse feces The garments of a typhus patient toward the end of his febrile course and for several days early in his convalescence are contaminated by large quantities of louse feces containing viable typhus rickettsiae Agitation of the garments disperses many particles of infected feces into the air of the room so that they may gain access to the respiratory tract or the conjunctivas of persons thus exposed It is possible therefore to become infected with typhus without being louse infested at any time

Morbid Anatomy The typhus rickettsiae invade the endothelial cells of small arteries capillaries and venules The affected cells tend to proliferate and the injury soon results in thrombus formation with small areas of necrosis and perivascular accumulations of phagocytic cells The lesions thus produced are sometimes referred to as typhus nodules and are scattered throughout the various organs and tissues particularly the skin the brain and the heart muscle

Bacterial bronchopneumonia is a frequent finding at autopsy in patients who did not receive specific therapy When penicillin or sulfonamides have been used an interstitial pneumonitis may be observed which is ascribed to the typhus rickettsiae themselves when death is delayed to the third week of the disease a necrotizing fibrinoid arteritis has been encountered which is similar to that found in numerous clinical conditions including hypersensitivity infection or renal disease (McAllister)

Pathological Physiology and Chemistry Although epidemic typhus has developed in millions of patients there have been remarkably few studies of the physiology and chemistry of this illness The explanation of the paucity of data lies in the association of typhus epidemics and human misery The disease breaks out under precisely those conditions which make hospitalization medical care and scientific investigation largely impossible

Suspensions of living fully virulent typhus rickettsiae are toxic for white mice producing death in a few hours This phenomenon has not been explained biochemically or physiologically Possibly the toxicity of rickettsiae is responsible for some of the clinical features of the disease On the other hand the widespread distribution of lesions in blood vessels can account for many of the manifestations of the illness in man

It is characteristic of typhus that a severe hypotension may occur often followed by evidence of renal insufficiency with a drop in urea clearance and a rise in blood urea nitrogen Oliguria and fixed specific gravity of the urine accompany the other findings If the patient recovers a diuresis is often noted concomitant with improvement in clinical condition

The plasma volume of several patients measured at various stages of typhus was found to lie within normal limits despite clinical impressions that dehydration was a feature of the clinical course in untreated cases Usually the hemoglobin and the plasma albumin values fall below normal and a rise in plasma globulin is observed particularly in the second week of the untreated disease (Yeomans)

When typhus occurs in a previously immunized person or when specific treatment is instituted early in the disease the abnormal findings described above may be entirely absent

Symptoms and Clinical Course *Untreated Nonimmunized Patients* The incubation period of typhus is approximately ten days to two weeks The onset may be preceded by variable prodromal symptoms such as lassitude headache and mild anorexia More often the onset is abrupt with a severe

headache and generalized aches and pains over the entire body The temperature rises in the course of two or three days to 40° C (104 F) and usually remains above this value for ten to fourteen days subsiding by rapid lysis in three or four days if recovery is to ensue (Fig 15) Death occurs between the ninth and the eighteenth days in about 20 per cent of patients (for all age groups) during epidemics

One or more shaking chills may occur at the onset Unproductive cough may be troublesome Constipation is more frequent than diarrhea Other symptoms and signs are sometimes present but the most constant and characteristic feature in the first week of illness is the severe headache which resists all attempts to alleviate it with the usual drugs

Toward the end of the first week the patient may appear to be slightly deaf His face may be flushed and dusky His conjunctivas are suffused and photophobia is usually apparent The pulse is often somewhat slower than is expected with a fever of 40 C or more The blood pressure is below normal A macular or maculopapular rash usually appears between the fourth and the seventh days (most commonly on the fifth day) on the back and chest spreading later to the abdomen and the extremities but sparing the face palms and soles except in severely ill patients

The lesions are 1 to 4 mm in diameter with somewhat irregular outlines and when first apparent are pinkish to reddish in color At first they fade on light pressure but later become fixed The rash lasts about as long as the fever rarely being visible in convalescence During the second week the lesions often become dark red or purplish as small hemorrhages occur in the lesions Frankly purpuric or confluent rashes are observed only in severe cases which usually end fatally

During the second week of typhus the pulse becomes more rapid The patient tends to be stuporous or to have bouts of active delirium followed by profound stupor This may progress to coma in severely stricken patients Skin necrosis over the sacrum and other pressure points may occur Otitis media and bacterial bronchopneumonia are frequent complications Gangrene of the toes the fingers the penis the scrotum the ear lobes or the tip of the nose may appear Parotitis sometimes bilateral often develops toward the end of the second week Pneumonitis may be present and is often found more easily by roentgenographic than by physical examination

Death from typhus usually occurs after gradual progression from stupor to coma Less often there may be peripheral vascular collapse with a fall in body temperature and death after a short period of unconsciousness Rarely a convulsion may bring an abrupt end to an illness which had not seemed particularly severe

Typhus Fever in Previously Immunized Persons The symptoms and clinical course of epidemic typhus are greatly modified as a consequence of active immunization which has been widely used in recent years since the development of formalin treated rickettsial vaccines "Adequate immunization" is defined in the section on Prevention and Control The clinical course in "adequately immunized" persons varies from an illness characterized only by a mild headache and slight fever of one or two days duration to an illness of several days with a rash consisting of a few macules which disappear in a day or two Complications are rare and the diagnosis often cannot be established except by laboratory tests The mortality is close to zero

Typhus Fever Modified by Specific Treatment Although clinical experience with the tetracycline drugs and chloramphenicol is less extensive in epidemic typhus than in scrub typhus and Rocky Mountain spotted fever the data at present indicate the probability of entirely similar beneficial results particularly if treatment is started early in the disease Thus any one of these drugs may be expected to arrest the clinical course of typhus at whatever stage is present when they are first administered They should bring about a drop in temperature to normal in thirty six to seventy two hours Clinical recovery depends on the rate of healing of the widespread vascular lesions of typhus which may take several days depending upon the extent of their development when therapy was begun

Diagnosis *Clinical Diagnosis* Before the characteristic rash appears it is impossible to assert on clinical grounds alone that a patient is suffering from epidemic typhus The early stages of several acute infectious diseases closely resemble the first few days of epidemic typhus—for example small pox relapsing fever malaria typhoid fever meningococcal infection yellow fever the other rickettsial diseases and so on The typhus rash is a distinguishing feature of considerable value the first lesions appear on the trunk and later spread to the ex

tremities sparing the face palms and soles except in severely ill patients This is helpful in distinguishing between typhus fever and Rocky Mountain spotted fever The typhus rash however is not present in 10 to 15 per cent of cases and may be difficult to recognize in dark skinned subjects The clinical diagnosis of epidemic typhus is particularly difficult in children or in persons who have previously received immunization In such instances a rash may be detected for short intervals only or may be entirely absent the symptoms are much less severe and the fever may persist for only a few days

Laboratory Diagnosis SPECIFIC SEROLOGICAL TESTS Agglutinins for typhus rickettsiae and complement fixing antibodies for specific rickettsial antigens appear in the serum of patients beginning about the end of the first week of the illness The titer rises toward the end of the illness and during the first and second weeks of convalescence tending to subside slowly thereafter In some instances persons recovered from typhus still show significant titers in their serum for months or years after an attack of the disease Sometimes on the other hand the specific antibodies may be no longer detectable a few weeks after the illness The use of killed rickettsial vaccines for active immunization often is followed by the development of specific antibodies which may add slight confusion to the interpretation of complement fixation tests taken during the course of a febrile illness The most important point in the serological diagnosis of typhus by specific rickettsial tests is the demonstration of a rise in titer from the early stage of the disease to a later stage A fourfold change in value is usually considered diagnostic

The rickettsial antigens prepared from infected yolk sac suspensions must be processed to eliminate a factor ordinarily present in the yolk sac which results in falsely positive complement fixation tests if the patient has positive serological tests for syphilis The antigens currently being prepared in this country are free of this cross reacting factor The specific antibodies for the typhus group serve to distinguish it clearly and definitely from the other rickettsial diseases Any laboratory which is able to perform routine complement fixation tests can purchase rickettsial antigens and perform specific diagnostic tests for the typhus group although the antigens are relatively more expensive than those for other tests

WEIL FELIX TEST Strains of the bacillus *Proteus vulgaris referred to* as OX 19 OX 2 and OX K have been relied upon in *the past for the* diagnosis of epidemic typhus As indicated in the Introduction *the basis of the* Weil Felix reaction with these strains of *P vulgaris* is an accidental occurrence of an antigenic component common to both Proteus and the rickettsiae Usually patients suffering from a disease in the typhus group develop agglutinins for Proteus OX 19 The titer rises from a low level to more than 1 160 in most instances Furthermore some of the members of the Rocky Mountain spotted fever group likewise agglutinate Proteus OX 19 Thus the test does not distinguish between the two groups As ordinarily performed the reaction is carried out in test tubes with either living or killed suspensions of *P vulgaris* in the smooth nonmotile form Slide tests developed by various workers are helpful during epidemics since the result may be obtained at the bedside in a matter of minutes with reasonable accuracy if suitable controls are performed

ISOLATION OF RICKETTSIAE FROM THE PATIENT The laboratory diagnosis of typhus may be made by inoculation of blood from a patient into susceptible species such as cotton rats guinea pigs or chick embryos if facilities are available for the further manipulations required to establish the identity of the microorganisms thus obtained The procedure is somewhat complicated and suitable only for specially equipped laboratories Colonies of human body lice may be used with success in the detection of living rickettsiae in patients Biopsy of skin lesions might also be of diagnostic help in the hands of an experienced pathologist

Prognosis The case fatality rate in epidemic typhus is less than 10 per cent in children As age increases the fatality rate rises until in persons over fifty it is 60 per cent or more However active immunization and the use of specific therapy greatly affect the mortality figures

In the absence of specific treatment the appearance of renal insufficiency is an early sign that a patient s illness will be severe or fatal The extent and severity of the typhus rash are roughly indicative of the severity of the disease Complications such as bronchopneumonia or gangrene of the skin are likewise serious prognostic signs A fall in systolic blood pressure to values below 80 mm of mercury for a few hours or longer may cause damage from which the patient may not recover even though the

blood pressure rises after the period of severe hypotension

When epidemic typhus occurs in persons who have received "adequate immunization" the prognosis is excellent unless the exposure to infection has been overwhelming

Treatment The tetracyclines and chloramphenicol are highly effective if administered early in adequate dosage by mouth The clinician must decide on the basis of his own preference which of these drugs he will use The initial dose for adults is 2 to 3 gm split into three parts at hourly intervals This should be followed by a maintenance dose of 0 5 gm every six hours until the patient s temperature is normal The dose may then be cut in half and continued for at least two or three days

If treatment is terminated too soon the fever and symptoms may recur but will respond promptly when antimicrobial therapy is resumed

Penicillin and streptomycin may have slight activity against typhus rickettsiae but their use in the clinical course of epidemic typhus should be considered only when secondary infections which respond specifically to penicillin or streptomycin are present The sulfonamides may have a harmful effect on the course of typhus and should not be given

Persons who handle typhus cases should be actively immunized A louse infested typhus patient on admission to the hospital should be bathed and dusted with DDT His garments should be sterilized It is not necessary to shave the patient in order to achieve satisfactory delousing with DDT

General Supportive Care Good nursing care is of great importance in the management of a patient with epidemic typhus A rise in temperature above 105 F is an indication for prompt administration of cold packs Barbiturates and morphine are to be avoided if possible Codeine may be tried for relief of headache but is likely to be ineffective It is expected that the use of the new antimicrobial drugs will so alter the clinical picture of typhus that many of the recommendations and precautions in general supportive care of patients will be obviated The reader is referred to the excellent account by Yeomans for further details in the management of epidemic typhus

Prevention and Control The accomplishments in prevention and control of epidemic typhus during World War II constitute a milestone in the history of preventive medicine Active immunization by means of killed rickettsial vaccines is now possible on a wide scale and has a profound effect on the severity and mortality of the illness "Adequate immunization" consists in an initial course of two subcutaneous inoculations of 1 ml each ten days to two weeks apart followed by stimulating doses of 1 0 ml each at intervals of a few months if exposure is expected The American military forces prefer the Cox type vaccine derived from the yolk sac membrane of developing chick embryos "Adequate immunization" probably reduces the *incidence* of typhus fever among exposed persons it definitely reduces the mortality close to zero and greatly lessens the severity of the illness

DDT as a 10 per cent powder effectively delouses large numbers of people quickly if the dust is blown up the sleeves down the neck and around the waistband with a hand duster or a power duster In recent years the human body louse in some areas of the world has become resistant to DDT Under these circumstances other insecticides must be relied upon for the elimination of louse infestation If our knowledge of prevention and control is properly applied it should be possible to eliminate outbreaks of typhus before they achieve serious proportions

BRILL ZINSSER DISEASE

(Brill s Disease Recrudescent Typhus)

History Nathan Brill after observing an epidemic of *typhoid* fever in the Mount Sinai Hospital in New York City subsequently encountered sporadic cases of an atypical typhoid like disease in which the Widal tests and blood cultures were negative In 1910 he reported 255 such cases and called attention to their several common features The disease usually occurred in immigrants from Russia or Poland there was no infectiousness (only in one household did a second case occur) headache fever and malaise were the prominent symptoms and the most characteristic aspect of the disease was a macular or maculopapular rash beginning on the fifth or sixth day Clinicians in other large cities of the eastern United States promptly reported cases which were referred to as Brill s disease In 1912 Anderson and Goldberger showed by cross immunity tests in monkeys that Brill s disease was a form of typhus

During the period from 1917 to 1932 the work of several investigators established the existence of two distinct varieties of typhus fever the first caused by *Rickettsia prowazeki* classic epidemic typhus spread from man to man by the human body louse the second caused by *R mooseri* the murine variety a disease in rats spread from rat to rat by the rat louse and the rat flea and occasionally transmitted from rat to man by the rat flea Since Brill s disease could not be ascribed to human lice or to rat fleas

	BRILL ZINSSER DISEASE	EPIDEMIC LOUSE BORNE TYPHUS
Past history of typhus	Yes	No
Occurrence of cases	Sporadic	Epidemic
Transmission	Cases can occur *without* lice	By infected lice
Usual duration of fever	7 to 11 days	12 to 18 days
Complement fixing antibody with specific *epidemic* antigen		
(a) On 8th day of illness	More than 1000	Less than 100*
(b) Maximal titer occurs	Between 8th and 10th day	Later than 12th day
Complement fixing antibody with specific *murine* antigen	Titer moderately high (usually 2 to 8 fold less than titer with epidemic)	Absent or low titer (at least 32 to 64 fold less than titer with epidemic)
Proteus OX 19 titers†	Usually less than 160	Usually from 320 to 5000

* Titers refer to denominators of serum dilutions
† By the concentrated antigen method (U S Army Medical Service Graduate School)

however this differentiation of typhus fever into louse borne epidemic and flea borne murine did not establish the position of Brill s disease as either one or the other It is unfortunate that many writers have erroneously used the term Brill s disease to describe sporadic cases of murine typhus

Etiology and Transmission In 1934 Zinsser and Ruiz Castaneda isolated typhus rickettsiae from three Brill s disease patients Their strains were similar to classic epidemic strains using the tests available for differentiation at that time On the basis of this information and his analysis of 538 cases of Brill s disease in Boston and New York Zinsser advanced his hypothesis that Brill s disease represents a recrudescence of an old typhus infection implying that the epidemic typhus rickettsiae once acquired remained latent for many years somewhere in the tissues of infected human beings According to Zinsser Brill s disease cases when occurring in louse infested communities might become foci of outbreaks of epidemic typhus thus over the centuries man might be the reservoir serving to maintain the disease between epidemics

Zinsser s hypothesis has been firmly established by recent studies Murray and Snyder have obtained seven new strains of typhus rickettsiae from cases of Brill s disease in New York Boston and Philadelphia By means of several laboratory procedures not available at the time of Zinsser s studies it has been conclusively shown that all seven new strains of Brill s disease rickettsiae are indistinguishable from classic epidemic strains Furthermore it has been clearly shown that human body lice become typhus infected by feeding on Brill s disease patients early in the disease Virulent typhus rickettsiae have been recovered by Price (Price and others 1958) from lymph nodes of two subjects many years after their original attacks of typhus

Loeffler and Mooser (1952) suggested the name Brill Zinsser disease in recognition of Zinsser s brilliant contribution to knowledge of this disease

Murray and co workers (1951) showed that Brill Zinsser disease occurred in Yugoslavia under conditions which precluded its explanation on the basis of transmission by body lice

The main differences between primary epidemic typhus and Brill Zinsser disease are listed in the accompanying table (from Murray and Snyder 1953)

Morbid Anatomy, Pathological Physiology and Chemistry, Symptoms and Clinical Course The findings in Brill Zinsser disease under these headings are the same as those described under Epidemic Typhus with the exception that the illness is somewhat milder and definitely shorter in duration

Diagnosis The clinical diagnosis of Brill Zinsser disease should be made when a fever of unknown origin occurs in a patient who has lived at some previous time in an area where typhus fever occurs in epidemic form who complains of an intense persistent headache and who has a macular or maculopapular rash on the fourth to the sixth day of the disease

The laboratory diagnosis should be made by the complement fixation test (or the rickettsial agglutination test) Recent studies have shown that the Weil Felix test should be ignored if negative

Prognosis and Treatment The statements in the paragraphs on *Prognosis and Treatment* of Epidemic Typhus apply to Brill Zinsser disease as well

Prevention and Control Since the factor or factors which precipitate an attack of

Brill Zinsser disease are not known nothing can be said in regard to prevention and control of this illness

MURINE FLEA BORNE TYPHUS FEVER

(*Endemic Typhus Rat Typhus Flea Typhus Urban or Shop Typhus of Malaya etc*)

History Murine typhus fever probably has occurred for centuries as a sporadic or endemic disease but only since 1931 has it been clearly distinguished from classic epidemic louse borne typhus Sporadic cases of typhus were reported occasionally in Europe in the medical literature before Brill s disease was defined as an entity Attention has already been called to the erroneous use of the term Brill s disease for cases of murine typhus a point which is again emphasized in the interest of clarity Indeed several of the papers which prepared the way for the final differentiation of epidemic from murine typhus refer by title to Brill s disease although the cases under discussion were murine flea borne typhus

In 1922 Hone reported several isolated cases from Australia and Wheatland described a noncontagious typhus like fever in the farm population of Queensland at a time when a plague of mice afflicted that part of Australia Maxcy concluded that typhus in the southeastern United States must have a reservoir other than man and he mentioned mice and rats specifically He further suggested that fleas mites or ticks could be the vector Mooser in 1928 observed a basic difference in behavior of certain strains of typhus rickettsiae in the tissues of guinea pigs Dyer and his colleagues isolated typhus rickettsiae from rat fleas in Baltimore (1931) and Mooser Zinsser and Ruiz Castaneda found the agent in rats in Mexico City Mooser then named the disease murine typhus to indicate its presence as a natural infection of rats Reports rapidly accumulated showing the world wide distribution of murine typhus The distribution of the disease in the United States is shown in Figure 16 (page 97) which shows the five year attack rates of murine typhus and also the distribution and rates for Rocky Mountain Spotted Fever Murine typhus has been reported from most of the states The total number of cases between 1931 and 1958 exceeds 40 000 The reported incidence was increasing up to 1946 the decrease since 1946 has been attributed in part to the control measures which have been vigorously applied in certain states

Etiology and Transmission Murine typhus fever is caused by *Rickettsia mooseri* This microorganism is similar to *R prowazeki* in size shape and staining properties The disease is maintained in nature as a mild infection of rats transmitted from rat to rat by the rat louse or the rat flea Neither the health nor the life span of the rat flea *Xenopsylla cheopis* is impaired by *R mooseri* once infected the rat flea probably continues to excrete *R mooseri* in its feces for the rest of its life The eggs laid by infected female fleas do not transmit *R mooseri* to the next generation of fleas Man usually acquires the disease when bitten by an infected flea In certain circumstances it is also possible that the ingestion of food recently contaminated by infected rat urine or flea feces may result in murine typhus

Unlike epidemic typhus murine typhus is maintained in nature independently of man by the rat flea rat transmission cycle The disease is not spread from one patient to another It has been reported that human body lice have been responsible for small outbreaks of murine typhus in which *R mooseri* has been transmitted from man to man in the same manner as described for *R prowazeki* This point cannot be settled until the more recently developed techniques for differentiation of epidemic from murine typhus rickettsiae are applied to the microorganisms involved in such outbreaks of presumed louse borne murine typhus The point is of great interest however since it has been postulated that murine typhus rickettsiae may change to the epidemic variety as a consequence of man louse man passage This must likewise be studied further before conclusions are justified

Morbid Anatomy Information on the morbid anatomy of murine typhus is limited but it is usually assumed that the lesions are essentially the same as those in epidemic typhus

Pathological Physiology and Chemistry Murine typhus has been even less well studied than epidemic typhus as regards abnormalities in physiology and chemistry No important qualitative differences between the two diseases are recognized the deviations from normal in murine typhus being relatively infrequent and small in extent

Symptoms and Clinical Course The incubation period of murine typhus lasts from six to fourteen days most often twelve days The symptoms are similar to those of epidemic typhus The principal differences between the clinical course of the two diseases are that murine typhus is milder and shorter the rash is less extensive and persists for shorter periods there are fewer complications and the case fatality rate is lower (less than 5 per cent for all groups)

It is impossible to distinguish an ordinary case of murine from a mild case of epidemic typhus solely on clinical evidence Although epidemiological considerations are valuable it should be emphasized that murine typhus is world wide in distribution and may occur in the same localities as epidemic typhus

Diagnosis *Clinical Diagnosis* The diagnosis of murine typhus is suspected when a patient has a sustained fever of several

days duration accompanied by headache generalized aches and pains and a macular rash appearing on the fifth or sixth day after onset of the fever The rash is first noted on the trunk and later spreads to the extremities the face palms and soles are not involved Since murine typhus is present in many of the places where Rocky Mountain spotted fever occurs it is helpful to recall that the rash of the latter disease usually appears on the exposed extremities first later involving the body and that it often appears on the face palms and soles The patient with murine typhus usually gives a history of activities likely to bring him into contact with places where rats are numerous a feature which is valuable in directing attention to the possibility of murine typhus Nevertheless a definite recollection of a flea bite is often absent

Laboratory Diagnosis The diagnosis of murine typhus is usually established by serological tests as indicated in the section on Epidemic Typhus The use of washed specific rickettsial antigens either in the complement fixation test or the rickettsial agglutination test permits the differentiation of epidemic from murine typhus Usually there is more than a twofold difference in the titer of the patient s serum against the two antigens the higher value being found against the homologous antigen Some difficulty may arise if the patient previous to the attack of typhus had received antityphus vaccine In such cases the titers may be identical Specific antibodies appear early in the second week of the disease increase in amount during the first part of convalescence and then subside slowly over a period of months Some persons have demonstrable antibodies for years after an attack of typhus

The Weil Felix test described earlier does not distinguish between murine typhus and Rocky Mountain spotted fever Consequently the more specific rickettsial tests are preferred

Rickettsia mooseri may be isolated from the blood of patients early in the disease by the inoculation of guinea pigs or rats The scrotum of male guinea pigs often becomes enlarged a few days after inoculation with *R mooseri* and the testes cannot be pushed back into the abdomen because there are adhesions between the layers of the tunica vaginalis This is called the Neill Mooser or the tunica reaction It is not specific for murine typhus however and is no longer regarded as the principal criterion for the differentiation of epidemic from murine typhus

Prognosis Murine typhus is usually mild with fatalities only in the older age groups The use of specific treatment is expected to reduce the severity of the illness

Treatment The comments on treatment as given in the section on Epidemic Typhus apply equally well to murine typhus

Prevention and Control The measures to prevent and control murine typhus are (1) use of DDT dust on rat runs to reduce the flea population of the rat colonies followed by (2) reduction of the rat population by poisoning trapping rat proofing buildings eliminating rat harborages such as trash or rubbish piles and the like

Vaccine suitable for human immunization is available and is recommended for persons who are likely to be exposed to murine typhus—for example personnel engaged in rat control programs or laboratory workers There is no justification for immunization of the general population since the attack rate is low and the measures for specific treatment are effective It should be noted that *murine* typhus vaccine is not effective against *epidemic* typhus and vice versa However an attack of either disease protects man against an attack of the other in most instances

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Rocky Mountain Spotted Fever

(Spotted Fever Tick Fever Tick Typhus [England] Fiebre Manchada [Mexico] Fiebre Petequial [Colombia] Febre Maculosa [Brazil])

Definition Rocky Mountain spotted fever is an acute specific infectious endangiitis chiefly of the peripheral blood vessels caused by *Rickettsia rickettsii* and transmitted by ticks It is characterized by an onset with chills continued fever of almost two weeks duration terminating in lysis severe pains in the bones and muscles headache and a macular eruption becoming petechial which appears after the middle of the first week on the wrists *ankles and back* and then spreads over the whole surface of the body

History The disease has probably existed in Idaho and Montana since the first settlement by white men and seems to have been known to the Indians before that time It was first described by Surgeon Major W W Wood in 1896 in a report to the Surgeon-General Maxcy of Idaho and McCullough of Montana gave the earliest clinical descriptions of the disease Important laboratory and field investigations were made by Wilson and Chowning and by Ricketts and his associates Ricketts established the transmission of the disease by the tick and defined most of the problems which have resulted in our present knowledge of the disease and its causation

Distribution Transmission and Incidence Rocky Mountain spotted fever is limited to the western hemisphere However closely related diseases occur throughout the world wherever *Ixodidae* have opportunity to feed on man these include boutonneuse fever of the Mediterranean basin South African tick bite fever North Queensland tick typhus and the tick borne rickettsioses of India and Russia Although the term "Rocky Mountain" is firmly fixed as part of the name for American spotted fever it now implies too restrictive a distribution of the disease This malady has been recognized throughout the United States except in Maine and Vermont as well as in Canada Mexico Colombia and Brazil No animal has been definitely incriminated as the reservoir for *Rickettsia rickettsii* but all small mammal hosts are suspect particularly rabbits and field mice Since the rickettsiae are transmitted transovarially by

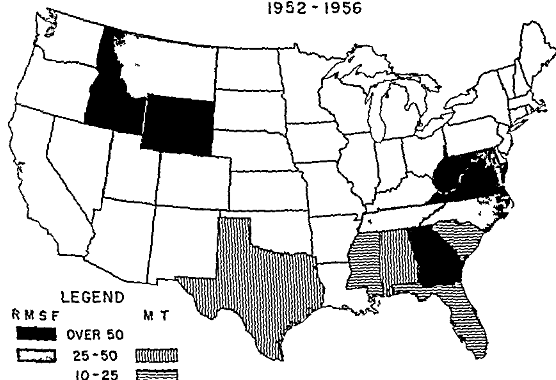


Fig 16 Incidence of spotted fever and murine typhus in the United States in recent years

certain ticks these vectors probably serve also as reservoirs

Ten species of ixodid ticks have been found infected in nature in the western hemisphere this by no means exhausts the list of potential vectors of the disease The seasonal periodicity of spotted fever in man in a given area is related to the life cycle of the local vector tick however the majority of cases occur in late spring and early summer

Almost 500 cases occurred each year in the United States from 1935 to 1949 inclusive with a mortality of about 20 per cent Following the introduction of specific antimicrobial therapy in 1948 the number of recognized cases decreased to about 300 annually and the mortality to nearly 3 per cent During the five year period 1952 1956 the highest attack rate per million population occurred in Wyoming but Idaho Virginia and West Virginia also had rates of over 50 per million Rates of 25 to 50 per million population were noted in Montana Utah Colorado Maryland North Carolina Tennessee and Georgia (see Fig 16) In the West where the wood tick (*Dermacentor andersoni*) is the vector a relatively higher proportion of adult males contract the disease On the other hand in the East where the dog tick (*Dermacentor variabilis*) is mainly responsible for transmission children and women are mainly affected Occupational propinquity to the vector is responsible for this distribution not variations in susceptibility of different ages and sexes

The mortality varies with age being higher in adults than in children Before the advent of specific chemotherapeutic measures the mortality rate for nonvaccinated adults in the Bitter Root Valley of Montana was about 80 per cent in contrast to 37 5 per cent for children Topping pointed out that approximately half the patients in the western states were over forty years of age whereas in the East about this same proportion were under fifteen years Little difference was noted in the fatality rates when patients from the two regions were compared on the basis of age

Etiology *Rickettsia rickettsii* (Wolbach) Brumpt the proved cause of Rocky Mountain spotted fever has a number of characteristics which distinguish it from the rickettsiae of the typhus and tsutsugamushi groups in addition to immunological differences Prominent among these are its cyclic morphology in ticks its hereditary transmission in ticks and its intranuclear as well as intracytoplasmic growth in tick and mammalian tissues It is distinguished from other rickettsiae of the spotted fever group by several types of immunological procedures Strains of *R rickettsii* vary considerably in their virulence for man and animals A toxin associated with the etiological agent is capable of killing mice within a few hours it is similar in many respects to the toxins of the typhus rickettsiae

Morbid Anatomy The distinctive pathological changes of spotted fever are found in the small vessels and are observed microscopically The gross changes often are unimpressive The following description is taken from Wolbach

> The blood vessel lesions consist at first of a proliferative reaction of the endothelium followed by thrombosis either mural or occluding A considerable degree of perivascular infiltration occurs The causal agent of the disease is found in endothelial cells and also in smooth muscle cells of blood vessel walls Arteries veins and capillaries are affected Minute focal lesions of the central nervous system accompanied by infarction of arterioles are common In addition diffuse infiltrations by mononuclear cells chiefly monocytes are found in the heart liver spleen and in the alveolar walls of the lungs Small areas of necrosis and considerable damage to the endothelium of the sinusoids are found in the liver

Pathological Physiology and Clinical Laboratory Findings Harrell points out that in fulminating disease with death early in the first week the picture is that of peripheral vascular collapse There is marked dilatation of capillaries and pooling of blood without increased capillary permeability or loss of fluid into extravascular spaces As the proliferative and thrombotic lesions develop in the small vessels anoxia occurs in the areas supplied with the usual resultant effects including necrosis In severe infections there is increasing capillary permeability with loss of water electrolytes proteins and erythrocytes This and other contributing factors result in a decrease in plasma volume and in serum proteins and chlorides along with an increase in thiocyanate space and even clinical edema Electrocardiographic changes consistent with edema and anoxia of the myocardium are found Liver function is diminished as evidenced by slight elevation of serum bilirubin and marked reduction of hippuric acid excretion after benzoic acid administration The elevated nonprotein nitrogen appears to be an extrarenal type of azotemia These various abnormalities intensify one another and set the stage for the development of terminal peripheral vascu

lar collapse With recovery whether natural or induced by antimicrobial therapy most of the physiological abnormalities are rapidly corrected however loss of edema fluid and restoration of serum proteins may take several weeks in the patient who suffered severe disease In the milder cases or in those given specific treatment early the physiological observations are minimal

The urine is that of any febrile disease Moderate leukopenia with neutropenia is frequent during the first few days eosinophils are decreased or absent Subsequently a mild leukocytosis appears with an increase in polymorphonuclear cells and a shift toward the left in the Schilling hemogram During the second week a normochromic normocytic anemia generally appears hemoglobin values of 9 gm and erythrocyte counts of 3 000 000 per cu mm are common The blood platelets remain within normal limits but the prothrombin time may become somewhat elevated late in the disease Increased capillary fragility is usually demonstrable by the tourniquet test The cerebrospinal fluid may be under slightly increased pressure and show a slight pleocytosis especially in patients with severe cerebral involvement Serological findings are discussed in the section on Diagnosis

Symptoms *Incubation* The incubation period of the more severe infections is two to five days and of the milder ones from three to fourteen days

Prodromal Stage Before the definite onset of the disease there may be a few days of malaise accompanied by chilly sensations and loss of appetite A prodromal stage is more evident in cases which prove to be relatively mild The onset is usually accompanied by a chill and there are severe general pains referred to the bones muscles back and joints particularly in the calf muscles large joints and lumbar region of the back Headache is common and severe The face is flushed the conjunctivas injected and the tongue white coated with moist edges and tip Constipation is usual There is usually photophobia



FIG 17 Rocky Mountain spotted fever Photograph of skin lesions taken two days before death. (Courtesy of Dr George E Baker Casper Wyoming)



FIG 18 Same patient as in Figure 17 illustrating coalescence of skin lesions which have become purpuric Localized areas of necrosis are evident (Courtesy of Dr George E Baker Casper Wyoming)

and there may be epistaxis A short dry cough is common The patient is frequently ill enough to take to bed on the second day of symptoms

Temperature Before the initial chill there may be a slight evening elevation of temperature After the chill the temperature rises fairly rapidly and reaches 102° to 104° F (38 8° to 40° C) by the second day In nonvaccinated persons who contract the disease *and do not receive specific therapy* the fever continues to rise gradually to a maximum of 104 to 105 F (40° to 40 5° C) during the second week In very severe cases in the Bitter Root Valley temperatures from 106° to 107° F have been recorded The maximum temperature persists in untreated patients throughout the second week of the disease with slight morning drops then falls by lysis so that normal temperature is reached before the end of the third week After recovery the temperature may be slightly subnormal for *a few days In fatal cases the temperature* may drop to normal or subnormal and then rise eighteen to twenty four hours before death which in severe cases usually takes place between the sixth and twelfth days of the disease

The *pulse* is at first full and strong but gradually loses volume and strength and increases in rapidity out of proportion to the fever During the height of the fever the blood pressure is markedly lowered as in typhus fever The pulse rate ranges from 110 to 140 and may reach 150 a few days before death A pulse rate of 120 with a temperature of 102° F is not uncommon Electrocardiographic changes occur (see section on Pathologic Physiology)

The *respiration* behaves very much as does the pulse It is rapid out of proportion to the apparent severity of the illness usually 30 to 40 a minute but increases occasionally to 60 before death

Eruption The rash appears most often on the third day of fever but may occur later during the first week or rarely on the second day Occasionally it may be preceded by a mottled appearance of the skin of the face neck and upper chest inconstant in appearance sometimes suggesting the onset of measles It appears first on the flexor surfaces of the wrists and ankles and back then on the forehead arms legs chest and abdomen The efflorescence requires twenty four to thirty six hours although the eruption may appear still later than this on the palms of the hands soles of the feet and scalp The mucosa of the cheeks palate fauces and pharynx may show the eruption The temperature is not appreciably affected at the time of the eruption but the subjective symptoms ameliorate The rash at first is in the form of rose-colored macules 1 to 4 or 5 mm in diameter not elevated not palpable and disappearing upon pressure The skin may be tender at the site of the spots The macules soon become deep red or purplish and increase in size often becoming confluent After a few days the rash *begins to persist upon pressure and then* becomes generally petechial Cutaneous and subcutaneous hemorrhages of considerable size occur frequently in severe cases and the skin in the second week of the disease may assume a glazed appearance Where the skin is thin as over the thighs a peculiar dusky reddish or bluish mottling may often be seen which is due to stasis of blood in the subcutaneous vessels because of thrombosis In mild cases the rash does not become confluent and the petechiae remaining small give a peculiar mottling *which several Idaho physicians have com*pared to the markings of turkeys eggs Slight icterus may appear in the second week of the disease

The rash begins to disappear with the subsidence of fever but may long be indicated by the persistence of pigmented spots Necrosis of the skin of the scrotum prepuce fingers toes vulva lobes of the ear and mucous membrane of the soft palate may occur in the third week *Desquamation* follows recovery but is slight except where the lesions have been most marked Minute cicatrices in the skin may persist for a long time after recovery In very mild cases the rash may be limited to one extremity In persons previously vaccinated *the rash may* be entirely absent

Neurological Symptoms Restlessness and insomnia are common throughout the disease constituting its most distressing features Hyperesthesia may be severe Delirium *is usual in severe cases during the* height of the fever and coma usually precedes death by a few hours or a day Rarely convulsions muscular rigidity and opisthotonus occur After recovery deafness visual disturbances slurring speech and mental confusion have been noted for a few weeks

Complications and Sequelae Secondary pneumonia is the one important complication and it is infrequent Circulatory failure and necrosis of tissue may be looked upon as resulting directly from severe pathological changes characteristic of the infection rather than as complications Harrell has drawn attention to evidence of residual

damage in the heart and brain of certain recovered patients

Immunity Recovery from Rocky Mountain spotted fever is accompanied by complete immunity for a long period of years According to Parker second infections have been reported eight or more years after the first in some instances ending fatally Guinea pigs recovered from feebly virulent strains are not fully protected against highly virulent strains Recovery from virulent strains does confer complete and lasting immunity in animals

A brief period of passive immunity may be conferred by the injection of blood from an immune animal

Active immunity can be produced by the injection of chemically killed rickettsiae the use of vaccine is discussed under Prophylaxis

Diagnosis Theoretically the same diseases must be considered in the differential diagnosis of Rocky Mountain spotted fever as in typhus but practically the seasonal incidence of the disease and its prevalence in certain geographical areas eliminate a number of possibilities *Meningococcal infections* and *measles* are the two diseases most liable to be temporarily mistaken for Rocky Mountain spotted fever Culture of the blood and cerebrospinal fluid should be resorted to when there is a question of meningococcal infection since the rash may simulate that of Rocky Mountain spotted fever Usually the more severe nervous symptoms with early rigidity of the neck and the character of the onset of meningococcal infection with meningitis should serve to differentiate the two Measles at its height in children presents difficulty for the rash may closely resemble the early rash of spotted fever The history of slower onset with coryza and lacrimation the presence of Koplik s spots the absence of severe muscular pains and the papular character and sequence of distribution of the rash are the most important differential data Typhoid fever with a pronounced rash may also have to be excluded The rash in typhoid fever however is more palpable and elevated than in Rocky Mountain spotted fever and is generally more restricted to the trunk A slower pulse rate lower fever diarrhea and positive blood cultures or a positive Widal reaction make final exclusion simple

Since Rocky Mountain spotted fever and endemic (murine) typhus coexist in at least twenty three states the problem of differential diagnosis often arises

Spotted fever is essentially a rural disease and exposure to ticks is important Most cases occur in the spring and early summer Endemic typhus transmitted by the rat flea is predominantly an urban disease in the United States but has a rural distribution in certain areas of the South where peanuts are cultivated It occurs most often in food handlers and peanut farmers whose premises are heavily infested with rats In contrast to spotted fever endemic typhus is more likely to occur in late summer and autumn

The outstanding clinical difference is in the evolution and distribution of the rash In endemic typhus it appears first on the chest and upper abdomen usually spares the palms and soles and rarely involves the face and neck wrists and ankles

Final differentiation of spotted fever from endemic typhus and also from epidemic typhus in some Latin American countries often requires the use of specific complement fixation tests This has become especially true since the introduction in 1948 of treatment with the antimicrobial drugs chloramphenicol and the tetracyclines now these diseases may be cut short so early in their courses that the typical clinical picture never develops

The Weil Felix reaction is of some value in the diagnosis of spotted fever All three types of *Proteus vulgaris* used (OX 19 OX 2 and OX K strains) may be agglutinated by the patient s serum most often the highest titer is obtained with the OX 19 strain but occasionally with the OX 2 strain A titer of 1 320 with a single convalescent serum is the lowest that can be considered of diagnostic importance but as in typhus a rising titer during the course of the disease is of greatest significance A test should be made as early as possible in the disease and repeated after the tenth day A significant reaction may not be obtained until convalescence has begun

A differential diagnosis between Rocky Mountain spotted fever and the other rickettsial diseases should not be attempted by means of the Weil Felix reaction *

The complement fixation technique using *Rickettsia rickettsii* as antigen provides a specific diagnostic test Complement fixing antibodies usually appear during the second or third week in patients who receive no specific therapy but may be delayed a week or so in those treated early in the disease No cross reactions are obtained with the typhus group but an appreciable number of cross sections occur with diseases of

* See Typhus Fever for further consideration of the Weil Felix reaction

the spotted fever group including mite borne rickettsialpox The more highly purified antigens give fewer cross reactions

Prognosis The prognosis has changed radically since the introduction of treatment with chloramphenicol and the tetracyclines Previously the over all mortality was about 20 per cent now deaths are rare in treated patients and are limited essentially to those who first receive specific therapy late in the course of the disease The prognosis in patients given only supportive treatment is best in vaccinated persons and in children and becomes progressively worse with advancing age or with secondary bacterial pneumonia

Harrell indicates the difficulty of estimating the prognosis in an individual early case but his classification of stages of severity of the disease is of interest Mild cases are those with negative tourniquet tests throughout the illness no edema and stable pulse and blood pressure Moderate cases show increased capillary fragility slight clinical edema tachycardia and toxic symptoms Severely ill patients exhibit marked purpura moderate edema delirium toxemia and vasomotor instability

Treatment The introduction since 1947 of the antimicrobial drugs chloramphenicol and the tetracyclines which are markedly effective in the treatment of rickettsial diseases including spotted fever has radically altered concepts of the therapy of this disease Early diagnosis and the proper use of these new antimicrobials generally render the patient afebrile in a few days and the severe disturbances of physiological mechanisms associated with the classic disease are prevented or minimized General supportive measures remain important however and their proper use in dangerously ill patients may tip the scale toward survival Harrell has emphasized the similarity between the peripheral circulatory collapse of spotted fever and shock associated with burns and trauma When such shock is present it should be treated vigorously in the usual manner replacement of blood proteins by administration of plasma and by whole blood transfusions and restoration of blood volume with saline and glucose solutions are indicated As in other forms of shock these procedures should be carefully regulated on the basis of results of frequent chemical studies of the blood Other general measures include those used for continuous fevers The barbiturates are indicated if restlessness and insomnia contribute to exhaustion Digitalis is rarely of value since the major circulatory disturbances are of extracardiac origin Penicillin is indicated in the presence of secondary bacterial pneumonia

Chloramphenicol or a tetracycline is given orally in 2 to 4 gm amounts as a "loading dose over a few hours followed by 2 to 4 gm daily in divided doses at six to eight hour intervals until the patient has been afebrile for a day or so In patients too ill to take oral medication an intravenous preparation of one of the antimicrobials may be employed for the loading dose Studies by Woodward s group at the University of Maryland and others (see Harrell) indicate that addition of cortisone to the usual chloramphenicol regimen produces a more rapid subsidence of fever and toxemia than antimicrobial therapy alone This combined therapy should be considered for critically ill patients A regimen of 200 mg of cortisone orally or intramuscularly followed by 100 mg doses at six hour intervals has been used for this purpose but cortisone should not be continued after the patient becomes afebrile or for longer than thirty six hours The minor untoward manifestations of treatment with the tetracyclines and chloramphenicol are well known as are the rare but serious blood dyscrasias associated with use of chloramphenicol Fear of neither type of toxic response should inhibit the physician from using these life saving drugs in spotted fever which if untreated has a high mortality a long convalescence and occasional sequelae

Prophylaxis General measures for control of the disease are directed toward reducing the chance of contact with infected vector ticks and immunization against the rickettsial agent

Recent advances have made personal prophylaxis the avoidance of tick bites more practicable than heretofore Brennan has found that clothing treated with N n butylacetanilide gives excellent protection against nymphs and adults of *Amblyomma americanum* Dimethyl phthalate one of the standard Army insect repellents has only a slight effect against ticks

Persons exposed in endemic tick infested areas should be carefully examined for ticks Daily stripping and thoroughly inspecting the entire body for ticks particularly about the hairline of the neck and the perineum is strongly recommended Children should be inspected twice daily The tick apparently cannot readily transmit the disease without having been attached for some hours

Ticks which have attached should be re

moved with care Applying ether chloroform or kerosene to a tick or holding a lighted cigarette near it may cause the arthropod to detach Otherwise forceps or tweezers should be used grasping the tick as close as possible to the point of attachment and applying gentle traction lest the mouth parts remain embedded in the skin Every effort should be made to avoid crushing the tick and contaminating the bite site with its contents Disinfect the area of attachment with soap and water and the wound proper with a toothpick dipped in crude phenol Silver nitrate and iodine are less effective

Measures for reducing the tick population have definite prophylactic value but because of their cost are rarely used primarily for the prevention of spotted fever in man Clearing and cultivation of infested land renders such areas safe Removal of ticks from live stock and dogs is an important control measure because these animals are regular hosts of adult *Dermacentor* This should not be done by hand A satisfactory dip for these animals is either 0 5 per cent chlordane or a combination of 0 025 per cent gamma isomer benzene hexachloride and 0 5 per cent DDT Dust sprays containing these insecticides may also be used None of these residual insecticides should be applied to cats which lick their fur and hence may be poisoned Campaigns for the destruction of small mammals which serve as hosts for the larval and nymphal ticks may be practicable in special circumstances particularly when directed against cottontail rabbits The rodenticide sodium monofluoracetate (Compound 1080) is most effective for this purpose but its high toxicity for men restricts its use to specialized personnel

Direct attack on the tick vectors by chemical means is feasible in selected instances Both DDT and chlordane give excellent control of *Dermacentor* and *Amblyomma* ticks when applied directly to the ground and to low vegetation in the form of solutions dusts or emulsions at the rate of about 2 5 pounds of either chemical to the acre In certain areas as in the northeastern United States 90 per cent of the local *Dermacentor* population is frequently found within 4 feet of roads and trails Most of this assemblage of ticks is often concentrated within a few inches of the trail margin

Vaccines containing chemically killed *Rickettsia rickettsii* are of value Immunization comprises a course of three injections given in the spring before ticks become plentiful Vaccination has been one of the most important prophylactic measures for those habitually or occasionally exposed to spotted fever It will no doubt continue to be useful for those at great risk but the availability of highly satisfactory therapeutic agents may be expected to reduce its need in those subjected to only slight risk of infection

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Scrub Typhus

(Tsutsugamushi Disease Mite Borne Typhus Japanese River Fever Tropical Typhus Rural Typhus)

Definition Scrub typhus is a self limited febrile illness of two weeks duration caused by *Rickettsia tsutsugamushi* transmitted by chiggers and distributed widely in the Asiatic Pacific area It is characterized by sudden onset of fever accompanied by a primary skin lesion (eschar) and by the development of rash on about the fifth day

History Scrub typhus may have been known in South China during the sixteenth century but the earliest recognizable description of the disease was by Hashimoto in 1810 He noted that the disease (tsutsuga) occurred along the banks of the Shinano River in Japan and that the natives of the area believed it to be caused by the bite of a minute insect or mite (mushi) Although it was extensively studied by Japanese investigators after its original description the interest of Western physicians remained dormant until the disease was recognized in Sumatra and Malaya about twenty five years ago

During World War II scrub typhus emerged from obscurity to occupy a position of great importance in military medicine Philip tabulated the cases in the Allied Armies in the Pacific Southeast Asia India areas during 1942–1945 and found 18 450 incidents of scrub typhus this tabulation is by no means complete The United States Army had 243 deaths among its 6685 men who contracted the disease

Distribution and Incidence Scrub typhus occurs along the coastal regions of Asia

from Korea to India and among the islands of the western and southern Pacific from Japan to northern Australia

There are no reliable statistics on inci dence of the disease in civilian populations in the Asiatic Pacific area however it is possible to arrive at certain estimates In the Shinano River area of Japan a survey made in 1947 among 2300 farmers whose occupation exposed them in infected fields during the mite season each year revealed 247 attacks during a total of 20 602 person years exposure This gives an attack rate in which the patient recovered of twelve cases per thousand farmers per year Be cause of limited geographical distribution of the disease in Japan the total number of cases is probably only a few hundred each year The disease is more common in parts of Southeast Asia than in Japan Selangor one of the states of the Federa tion of Malaya with an area about two thirds that of Connecticut and a population of about 400 000 reported 162 cases of typhus with 3 deaths in the first eight months of 1948

High attack rates were attained during brief periods in certain Allied military groups during World War II Among Ameri cans at the Sansapor beach head in the Southwest Pacific 403 men of one regiment suffered the disease between the sixth and twentieth days after landing moreover the attack rate during the second week at Sansapor reached 900 cases per thousand troops per year Similarly 18 per cent of one British battalion contracted scrub ty phus during two months in Burma in 1944 and 5 per cent of the total strength died of the disease

The mortality in scrub typhus has varied widely in different geographical areas and in different populations The highest rates have been in Japan where 40 to 60 per cent of the diagnosed patients have suc cumbed In Malaya during the past twenty years about 7 per cent of the cases ter minated fatally Even in the same general area and in a relatively homogeneous popu lation viz United States Army personnel in the Southwest Pacific the case fatality ranged between 0 6 and 35 per cent for the outbreaks at Owi Biak and Finchaven respectively Many factors undoubtedly con tribute to the variations in mortality of scrub typhus but it is well established that certains strains of *Rickettsia tsutsugamushi* are more virulent than others for laboratory animals and presumably this is also true for man

Epidemiology Scrub typhus is transmitted to man by at least two species of mites *Trombicula akamushi* and *T deliensis* Only the six legged larvae are parasitic on mammals and birds The nymphs and adults both of which have eight legs also live in soil and vegetation but presumably feed on eggs of mosquitoes and other in sects The tiny (0 15 to 0 4 mm) red larvae attach themselves to the skin of the host and obtain a feeding of lymph or tissue juice During the attachment infected lar vae may transmit *Rickettsia tsutsugamushi* to the host or uninfected larvae may ac quire rickettsiae from a host with active disease The rickettsiae apparently main tain a symbiotic existence in the mite since their presence does not interfere with the development and propagation of the arth ropod In several of the *Trombicula* rick ettsiae are transmitted transovarially from one generation to the next Thus the mite serves both as the vector and as a reservoir of the causal agent Various small rodents constitute the animal reservoir In different regions these include rats voles shrews and field mice

Endemic areas of scrub typhus occur in different types of terrain but are found most often in fields which through neglect have been permitted to become overgrown with scrub vegetation The essential fea tures of an endemic focus are (1) adequate ground moisture and warmth for the propa gation and emergence of vector mites (2) suitable rodent population and (3) the presence of *R tsutsugamushi* in rodent hosts and vectors of the area Because of the exacting requirements for a focus the endemic areas are often sharply delimited small islands of infection which present the same general appearance as surrounding uninfected terrain Birds serve as hosts for vector mites and may help seed infection in nearby or distant areas

Man is an incidental host for *Trombicula* He contributes to the cycle of scrub typhus in nature by modifying the ecology of the region and thus influencing the rodent and mite populations His occasional inad vertent infection with *R tsutsugamushi* is unimportant in the maintenance of either the disease or endemic areas

The seasonal incidence of human disease is dependent on the prevalence of mites In the classic scrub typhus areas of Japan it is in the summertime that *T akamushi* emerge and become numerous However in certain Japanese islands where *T scutel laris* is presumed to be the vector cases of scrub typhus occur in winter In the sub tropics and tropics cases occur throughout

the year whenever susceptibles are introduced into an endemic area but infections are more prevalent during the wet seasons

Etiology *Rickettsia tsutsugamushi* (Hayashi) Ogata the etiological agent of scrub typhus is an intracellular obligate parasitic microorganism It has the general properties of other rickettsiae pathogenic for man but is distinguished from them by its host range and by its specific immunological properties Strains of *R tsutsugamushi* vary in their virulence for animals and several strains yield a toxic material which in concentrated form kills mice within a few hours All strains have certain specific antigens in common but the results obtained with a variety of immunological techniques indicate that the species *R tsutsugamushi* is not antigenically homogeneous The growth of *R tsutsugamushi* in experimental animals is inhibited by a number of chemical substances The three which have proved of value in the treatment of patients with scrub typhus are para amino benzoic acid chloramphenicol and the tetracyclines

Morbid Anatomy Macroscopic changes found at autopsy are not striking The primary eschar may be present but no rash is seen The body cavities contain moderate amount of serofibrinous fluid and the parenchymatous organs show cloudy swelling The spleen is enlarged and there is generalized lymphadenopathy Hemorrhagic pneumonia is usually present with superimposed secondary bronchopneumonia

The basic histological lesions in scrub typhus as in other rickettsial diseases are disseminated focal vasculitis and a perivasculitis consisting of accumulations of monocytes plasma cells and lymphocytes Acute nonsuppurative myocarditis and encephalitis and an interstitial pneumonitis are found in almost all fatal cases

Clinical Laboratory Findings There are no specific cytological or chemical changes in the blood in scrub typhus During the first week of illness the total leukocyte count is normal or moderate leukopenia occurs leukocytosis generally indicates secondary bacterial infections Anemia is rare but the erythrocyte count often becomes reduced slightly during the disease In severely ill patients the plasma proteins may be moderately reduced Plasma fibrinogen may be decreased in patients with impairment of hepatic function and the serum bilirubin may be slightly elevated Profuse sweating and an inadequate intake of water and salts may produce disturbances of acid base equilibrium

Rickettsia tsutsugamushi can be recovered from the blood of patients throughout the first ten or twelve days of fever The agent is demonstrated indirectly white mice inoculated intraperitoneally with the blood sample acquire typical disease and rickettsiae are found on microscopic examination of stained smears of their peritoneal scrapings Late in the second week agglutinins for the OX K strain of *Bacillus proteus* appear in the patients blood

Symptoms After an incubation period of six to eighteen days generally ten to twelve illness begins suddenly with headache feverishness and intermittent chilliness The conjunctivas are injected there is generalized lymphadenopathy and in the majority of Caucasians a primary lesion or eschar at the site of attachment of the infected mite may be found The temperature may increase stepwise during the first week to levels of 104 to 105 F or it may rise abruptly to such levels on the first or second day and remain elevated About the fifth day a red macular rash appears on the trunk and may extend to the arms and legs It usually persists for several days but may disappear within a few hours The rash like the eschar is more often absent than present in Asian patients with scrub typhus

The pulse during the first week is relatively slow usually 70 to 100 per minute Nonproductive cough is commonly present and rales and rhonchi are generally heard Roentgenographic evidence of pneumonitis is found in about one fifth of the patients Despite the sustained high fever the severe discomfort from headache and the apathy patients rarely appear dangerously ill during the first week

The temperature remains elevated during the second week and even the less severely affected persons begin to show the debilitating effects of sustained illness The relative bradycardia is often replaced by a pulse rate in proportion to the fever or even higher and the systolic blood pressure drops below 100 mm of mercury These findings together with evidence of peripheral circulatory failure are bad prognostic signs Other manifestations of severe disease are signs of involvement of the central nervous system such as delirium stupor and muscular twitchings Frank signs of pneumonia may develop

At the end of the second week the temperature falls by lysis and remains normal after the fourteenth or fifteenth day With the reduction in fever the pulse rate and blood pressure return to normal levels

The eschar is practically healed Convalescence is protracted in patients who fail to receive antimicrobial therapy and full return to mental and physical vigor is usually delayed for several months Sequelae in the form of nervous or psychiatric disorders and permanent damage to the heart are rare

Immunity Patients who recover from scrub typhus are resistant to reinfection with the homologous strain of *R tsutsugamushi* for some years However within two months after recovery reinfection with a heterologous strain causes mild disease and after one year typical scrub typhus Among the 223 Japanese farmers who gave a history of scrub typhus in the survey mentioned previously 19 suffered a second attack and 5 had a third attack The interval *between attacks varied from two to forty* four years with an average of seven years Convalescent patients exhibit specific neutralizing and complement fixing antibodies Despite their presence however *Rickettsiae tsutsugamushi* persist in the tissues of mice and men for months after clinical recovery

Diagnosis The geographical distribution of scrub typhus assists in differentiating this disease from other rickettsial infections Epidemic typhus is absent from the warm regions where most scrub typhus is found In Southeast Asia murine typhus (flea borne urban typhus) is the rickettsial infection most apt to be confused with scrub (rural) typhus The history of recent exposure in town or country the finding of the scrub typhus eschar and the results of serological tests during the second and third week serve to differentiate these two diseases Agglutinins against the OX K strain of *Proteus vulgaris* appear in the serum of patients with scrub typhus and against the OX 19 strain in murine typhus Finally negative results with the specific complement fixation tests for epidemic and murine typhus and for spotted fever and recovery of *Rickettsia tsutsugamushi* from the blood of the scrub typhus patient confirm the diagnosis The presence in convalescent serum of specific complement fixing antibodies which react with antigens containing *R tsutsugamushi* is of diagnostic importance Negative results are of no significance however since the antigenic heterogenicity of strains of scrub typhus is such that only a proportion of patients exhibit antibodies which fix complement with the available antigens

Differentiation of scrub typhus during the first week of illness from typhoid fever malaria dengue infectious hepatitis leptospirosis and fevers of unknown origin is difficult Headache conjunctival injection and lymphadenopathy are more conspicuous in scrub typhus The eschar and rash if present are of some aid but the early primary lesion may be confused with cutaneous infections which are common in the tropics The sustained fever in the second week the development of the black necrotic center in the eschar and negative results in laboratory tests for typhoid fever and malaria point to scrub typhus The dramatic improvement within a matter of hours after chloramphenicol or a tetracycline is given to scrub typhus patients is helpful in eliminating most of the nonrickettsial diseases under consideration

Prognosis Patients with evidence of circulatory failure encephalitis or frank *pneumonia should be considered gravely* affected Death when it occurs usually happens during the second week and is attributable in about equal numbers of cases to the three manifestations just mentioned The disease is rarely lethal for children but fatalities increase in proportion to age and elderly persons usually die The variations in mortality in different areas have already been discussed

The prognosis has changed radically since the introduction of chloramphenicol and the tetracyclines in the therapy of this disease Even the gravely ill and the aged patients now recover under treatment

Treatment Chloramphenicol and the tetracycline drugs are highly effective in scrub typhus There is no choice among them and each is given orally as follows a "loading dose" of 3 to 4 gm is administered either at one time or over a few hours and followed by 1 gm amounts at eight hour intervals until the patient is afebrile On this regimen general improvement is evident in twelve hours and the patients are afebrile in thirty hours on the average As the temperature becomes normal headache disappears appetite returns and the mental apathy is lost Critically ill patients may not become permanently fever free for forty-eight to ninety six hours

If treatment is begun within the first few days of disease a 3 gm supplementary dose of the drug used should be given about the eighth day after onset to prevent relapse which occurs in about three fourths of such patients A supplementary dose is not required in patients who are first treated on the seventh day or later since immunity in scrub typhus which begins to develop late in the second week is adequate in these patients by the time the drug effect is lost While mild untoward manifestations

not infrequently result from administration of the tetracyclines and chloramphenicol and severe blood dyscrasias may occur very rarely the value of these drugs in scrub typhus is so great and the disease so severe that they should be employed without hesitation

Since the introduction of specific therapy the severe manifestations of scrub typhus are generally brought under control so rapidly that little is needed in the way of supporting therapy For those *in extremis* at the time of admission to the hospital parenteral fluids transfusions or oxygen therapy may be indicated Treated patients are now given a full hospital diet within a few days after becoming afebrile are allowed to sit up a few days later and are usually discharged after a week of normal temperature They are permitted to return to light work shortly thereafter Before the introduction of specific treatment military patients were allowed to convalesce from one to four months before being returned to duty

Prophylaxis Vaccines containing killed *Rickettsia tsutsugamushi* have not been successful in preventing disease in persons exposed under field conditions It is assumed that the antigenic variations in strains of scrub typhus organisms are mainly responsible for the failure to protect man during field exposure

Personal prophylaxis by avoidance of mites depends primarily on the use of mite repellents and miticidal agents such as dimethyl or dibutyl phthalate or benzyl benzoate The phthalates are smeared by hand on the clothes and exposed surfaces of the skin (avoiding the eyes and crotch because of the burning sensation produced by the chemical) Impregnation of clothes with benzyl benzoate is attained by dipping the garment in an aqueous emulsion of the substance When properly used the mite repellents are highly effective in preventing scrub typhus They are relatively expensive and require constant intelligent use short periods of carelessness during exposure in hyperendemic areas result in infection

Clearing and cultivation of endemic areas of scrub typhus eventually free them of hazard by reducing or destroying the vector mites and rodent reservoirs

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Rickettsialpox

Definition Rickettsialpox is a mild self limited acute febrile illness caused by *Rickettsia akari* and characterized by an initial skin lesion developing at the site of infection fever of about one week s duration and a papulovesicular rash

History Distribution and Epidemiology Rickettsialpox was first recognized in New York City in 1946 although it undoubtedly existed there earlier From 140 to 180 cases have been reported annually in New York City since that time A few cases have been diagnosed in other portions of the United States and outbreaks have been reported in European Russia

The brilliant work of members of the U S Public Health Service and the New York City Department of Health resulted in isolation of the causal agent from the blood of patients and its identification as a distinct rickettsial species and in the elucidation of the epidemiology of the disease Rickettsialpox is transmitted by a small colorless mite *Allodermanyssus sanguineus* (Hirst) which normally infests mice and small rodents House mice serve as a reservoir of infection The etiological agent has been recovered from mice and mites collected from houses in which patients acquired the disease

Etiology *Rickettsia akari* the etiological agent of rickettsialpox has the general morphological and biological characteristics of other rickettsiae It is antigenically related to but distinct from *R rickettsii* which causes Rocky Mountain spotted fever White mice guinea pigs and embryonated eggs are susceptible to experimental infection Diagnostic antigen for use in the complement fixation test with human serum is prepared from yolk sacs of infected chick embryos

Morbid Anatomy No deaths have been attributed to rickettsialpox however skin lesions have been removed surgically for histological examination The initial lesion of rickettsialpox resembles the primary lesion of scrub typhus The histopathology of the early maculopapular rash of rickettsial pox consists in changes in the vessels of the corium and perivascular accumulations of mononuclear cells The vesiculation which develops in the maculopapular lesions of rickettsialpox is unique among the rickettsial diseases Necrosis of epithelial cells results in an intra epidermal vesicle superimposed on the papule

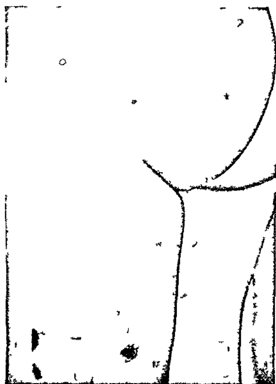


FIG 19 Vesicular eruption of rickettsialpox with initial lesion visible on posterior aspect of left thigh (Courtesy of Dr Harry M Rose)

Symptoms The period between the bite of the infected mite and the appearance of the initial lesion at this site is from one to two weeks Three to seven days after the lesion develops the febrile phase begins The rash may accompany the fever but more frequently appears several days later

The initial lesion begins as a firm red papule which increases to a diameter of 1 to 1 5 cm After a few days the center becomes vesiculated the papule is surrounded by a zone of erythema and the regional lymph nodes are moderately enlarged The clear vesicular fluid becomes cloudy and dries and a black eschar is formed The lesion which is not painful heals slowly the scab drops off about the third week leaving a small scar

The febrile phase begins with sudden onset of chills or chilly sensations sweats headache muscle pains anorexia and photophobia The temperature frequently reaches 103° to 104° F and remains elevated with morning remissions for approximately one week

The maculopapular vesicular rash is generalized in distribution and may be abundant or scanty Lesions occasionally involve the oral mucosa but rarely the palms and soles The exanthema runs its course in about a week the vesicles dry and the scabs fall off leaving a transient discoloration but no scar

Other findings are essentially limited to those associated with a febrile disease although the spleen is palpable in some cases *Complications* are rare

Laboratory Findings The usual laboratory examinations reveal a moderate leukopenia and the findings which are associated with a febrile illness The erythrocyte sedimentation rate may be slightly elevated

During convalescence specific complement fixing antibodies which react with antigens containing *Rickettsia akari* appear in the serum of patients The Weil Felix test which becomes positive in patients with most rickettsial diseases remains negative in rickettsialpox

Diagnosis Chickenpox has been most frequently confused with rickettsialpox The following points help to differentiate the two diseases Rickettsialpox occurs in persons of all ages and has an initial lesion fever generally precedes the rash the vesicle surmounts the papule which is discernible throughout the exanthema and finally diagnosis can be established by a specific serological test In contrast chickenpox is usually a childhood disease and has no initial lesion the rash appears at the height of the fever and the papular cutaneous lesion is entirely transformed into a vesicle

The lesion of the papulovesicular stage of smallpox resembles that of rickettsialpox but the exanthema is generally more abundant in variola The constitutional reaction in smallpox is greater than in rickettsialpox but it also precedes the rash Finally the variolar vesicles progress to pustules

The rashes of the typhus fevers and of the other members of the spotted fever group of the rickettsial diseases are not vesicular the febrile periods of these diseases are more prolonged than in rickettsialpox and the illnesses are more severe with appreciable mortality rates The Weil Felix reaction and specific complement fixation tests using rickettsial antigens are positive Cross reactions are obtained with serum from patients with Rocky Mountain spotted fever and rickettsialpox when complement fixation tests are used However if highly purified and washed rickettsial antigens prepared from the two causal rickettsiae are used in the test a definite serological diagnosis can be made

Treatment Symptomatic treatment has been used in this mild self limiting disease Dramatic improvement follows the use of chloramphenicol or the tetracyclines

oral doses of 2 to 4 gm daily render the patient afebrile and essentially free of complaints in forty-eight hours

Prophylaxis Control measures consisting in elimination of house mice and vector mites have been attempted in certain of the housing projects in New York City where multiple cases occurred

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Q Fever

Definition Q fever is an acute self limited illness characterized by abrupt onset high but somewhat irregular fever headache and in many instances pneumonitis similar to that of primary atypical pneumonia The first few cases of this disease were called Query fever and from this designation the final name Q fever evolved (Derrick)

Etiology Q fever is caused by the microorganism *Coxiella burnetii* which is named for Burnet who first recognized it in Australia and for Cox who described it in the United States *Coxiella burnetii* resembles the other rickettsiae in size shape and staining properties but it differs in certain respects for example it is more resistant to adverse physical and chemical factors than the other rickettsiae An important feature is that *C burnetii* is the only rickettsial species which infects man without producing a macular or maculopapular rash Furthermore agglutinins for the *Proteus* group do not appear in human or animal serums as a consequence of infection with *C burnetii* In the febrile stage of Q fever the microorganisms have been recovered from the blood urine and sputum of patients by appropriate laboratory procedures

Distribution and Transmission Q fever has been reported from Australia the United States Panama Europe the Middle East North and Central Africa possibly India and China It is therefore potentially world wide in distribution The manner in which the disease is usually acquired by man is probably by inhalation of desiccated Q fever rickettsiae derived from various sources

Q fever rickettsiae have been found in the milk of naturally infected cattle sheep and goats in the placentas of cattle and sheep and in the feces of sheep The presence of huge numbers of Q fever rickettsiae in these locations usually is not associated with any evidence of illness of the animal Pasteurization of milk is not completely effective in destroying the viability of Q fever rickettsiae in milk which has been heavily contaminated Furthermore Q fever rickettsiae have been demonstrated in dust laden air at dairies in California Butter made from contaminated milk may contain viable Q fever rickettsiae

In the United States human infections have been reported from many areas particularly California Montana Texas and Illinois Occupational exposure has been related to the occurrence of cases for example in laboratories where the Q fever rickettsiae are cultivated and in dusty environments where wool is processed On the basis of serological tests it is estimated that several thousand persons had Q fever in southern California in recent years The disease is only rarely acquired by contact with patients suffering from Q fever this fact is remarkable in view of the pneumonitis which is a feature of many of the cases It should be noted that *C burnetii* has been found in certain ticks but that only a few human cases of Q fever have been attributed to contact with infected ticks

Morbid Anatomy Few fatal cases of Q fever have been reported and in most of these autopsies were not performed Consequently satisfactory data are not available for general remarks on the pathology of Q fever The reader is referred to the articles by Lillie Perrin and Armstrong and Whittick

Pathological Physiology and Chemistry The abnormalities in physiology and chemistry noted in Q fever are those which usually accompany mild fevers of diverse etiology Transient albuminuria and elevated sedimentation rates have been reported The erythrocyte count and concentration of hemoglobin are usually normal and the total leukocyte count is often within

normal limits Changes in the differential count have been noted but are without diagnostic significance

Symtoms and Clinical Course The incubation period of Q fever is two to three weeks In several outbreaks the onset occurred abruptly but there are numerous cases in which the disease began insidiously Malaise chilly sensations headache anorexia and weakness are usually the first symptoms noted The *temperature* rises more or less abruptly to 39° C or higher There are usually wide fluctuations in temperature particularly if salicylates are administered The fever persists for a few days in mild cases or it may last for two weeks in severe cases The *pulse rate* tends to be somewhat elevated more or less in proportion to the fever Generalized muscular aching is frequent Retro orbital pain is usually noted and is sometimes accompanied by photophobia In some cases there may be severe and sharply localized pain which either shifts from one site to another or persists for only a few hours

Toward the end of the first week of illness *a dry cough develops in more than* half the patients This may be accompanied by mild to moderate chest pain In a few patients the cough may become productive of small amounts of sputum occasionally blood streaked Despite the cough and chest pain few patients have symptoms or signs of upper respiratory involvement as part of the Q fever syndrome *The* rate of respiration ordinarily is not elevated Furthermore physical examination of the chest may reveal nothing to indicate the presence of pneumonitis which is the characteristic feature of Q fever although fine crepitant rales may reward a careful search In nearly all cases however roentgenographic examination indicates the presence of patchy areas of consolidation involving only small portions of the lobe A single lesion is the usual finding but multiple involvement has been noted Ordinarily the lesions are in the lower lobes but they may occur in any lobe It is difficult or impossible to distinguish these findings from those which are present *in atypical pneumonia or psittacosis* No correlation has been observed between the extent of pulmonary involvement as judged from the roentgenogram and the severity of the clinical course The pulmonary lesions sometimes may be found by roentgenogram when the patient is convalescent

The illness *usually* ends with complete recovery and the period of convalescence ordinarily is brief but relapses have occurred in several instances they are similar to the primary disease and may be mild or severe The possibility of chronic infection with Q fever has been raised this question needs careful study It is probable that there have been many human cases of Q fever so mild as to escape medical attention

Diagnosis The clinical diagnosis of Q fever should be considered when a patient has a febrile illness with anorexia weakness severe headache and roentgenographic evidence of a patchy pneumonitis The absence of symptoms or signs of upper respiratory tract involvement is helpful The presence of pain in the eyes or of photophobia is a further aid A prompt response to specific therapy with tetracycline or *chloramphenicol may assist the clinical* diagnosis The final diagnosis is usually established by laboratory tests however particularly by a rise in titer of complement fixing antibodies in the patients serum early in convalescence It is *not* advisable to attempt isolation of *Coxiella burnetii* from a patient by inoculation of *animals since this procedure usually re*sults in infection among the laboratory personnel The Weil Felix reaction and the cold agglutinin test are negative in Q fever

Prognosis The case fatality rate in Q fever is very low The appropriate use of a tetracycline or chloramphenicol early in the illness should improve the prognosis

Treatment *The tetracyclines or chloram*phenicol may be used for Q fever On the basis of present evidence any of these drugs may be expected to arrest the illness promptly Relapses may be anticipated if therapy is terminated too soon after the fall in temperature These agents should be given in the same dosage for Q fever as for *Rocky Mountain spotted fever or epidemic* typhus (see pp 93 102)

Prevention Preventive measures include the pasteurization or boiling of milk from cows goats and sheep Vaccination of man with killed suspensions of Q fever rickettsiae affords protection against exposure to infection via the respiratory tract under *certain circumstances* (Tigertt and Benenson 1956) These writers reported that a single ml of vaccine given early in the incubation period to previously unvaccinated men prevented or delayed the onset of clinical disease For the infected patient only one precaution is recommended namely the sterilization of sputum and excreta

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Trench Fever

(Quintan Fever Shin Bone Fever Wolhynian Fever His Werner Disease etc)

Definition Trench fever is a specific exanthematic louse born infection characterized usually by a sudden febrile onset with pain and soreness in muscles bones and joints The disease is never fatal

History The disease was first recognized in 1915 when it appeared on the Western and Eastern fronts during World War I It constituted one of the major medical problems of World War I and was investigated intensively by a British and by an American commission After demobilization the disease practically disappeared It reappeared during World War II but on a relatively small scale

Epidemiology and Etiology The responsibility of the body louse in transmitting the disease to man was established by both British and American commissions as a result of well controlled louse feeding experiments upon human volunteers The infective agent is present in the excreta of lice where it may remain infective for several months The disease is transferable from man to man by intravenous inoculation of blood

As for the etiological agent there is strong but perhaps not conclusive evidence incriminating an organism (*Rickettsia wolhynica R pediculi R quintana*) the presence of which in the intestines and feces of lice was definitely correlated with infectivity by Bacot Arkwright and Duncan The organism occurs extracellularly in the gut of the louse thus differing from other pathogenic rickettsiae Mooser and Weyer have transmitted the infection to *Rhesus* monkeys in which it is subclinical and demonstrable only by the fact that lice fed on infected monkeys become intestinal carriers of the rickettsia No other experimental animal has been shown to be susceptible

Morbid Anatomy Postmortem studies have not been made since the disease is never fatal Examinations of excised macules from the skin have apparently shown no important specific changes The spleen is usually enlarged and firm to palpation Rickettsiae have not been satisfactorily demonstrated in human tissues

Symptoms *Incubation Period* Experimental evidence indicates that the usual incubation period is ten to twenty days with extreme limits of five to thirty-eight days

Onset The onset is usually acute with chills and a rise in temperature to 102 or 103 F Severe headache usually behind the eyeballs and complete anorexia are almost constant at this stage Nausea and vomiting sometimes occur Laryngitis and bronchitis may be present but are rarely severe Perhaps the most characteristic symptom is severe "myalgic" pain in various parts of the body but most prominent in the lumbar region and legs There are also muscular soreness pain on rotating the eyeballs conjunctivitis and photophobia Occasionally the onset is insidious with symptoms of neurasthenia and tachycardia

Course of the Disease The progress of the disease is remarkably variable The fever and symptoms may last only two or three days or may be typhoidal in character lasting two or three weeks A common form is that in which there are two febrile periods of three to five days each with twelve to twenty four hours of remission between them Again there may be short febrile periods of only twenty four to thirty hours recurring regularly every five days for a variable period of time Relapses are prone to occur several weeks or months after apparent recovery

The characteristic *rash* usually appears during the first twenty four hours and thereafter comes and goes with fever even in the case of late relapse It is composed of red macules 2 to 10 mm in diameter appearing first on the chest and abdomen and usually confined to those regions although they may involve the entire trunk The extremities are occasionally involved but the face always escapes

The pulse rate during the initial acute attack is increased in proportion to the fever but may be relatively much higher in late relapses A sharp increase in the pulse rate often precedes and may be the only objective evidence of a relapse

Pain and soreness in the muscles usually recur with each febrile relapse Lumbar

pain is most apt to persist in the chronic stage of the disease Abdominal pain and tenderness probably of muscular origin are usually bilateral and more pronounced on gentle than on firm pressure This fact together with the palpable spleen rash and generalized pain and tenderness usually serves to differentiate the condition from appendicitis

Prognosis The disease has no known mortality Its duration is extraordinarily variable but about 85 per cent of all patients are able to return to work within two months of the time of onset It is believed that in about 5 per cent of all cases the disease becomes chronic necessitating a much longer period of time for complete recovery Recovery is apt to be delayed in the aged and in the debilitated

Diagnosis During epidemics typical cases are readily diagnosed on the basis of the symptomatology The atypical abortive cases may be confused with influenza in the absence of the characteristic rash The mild respiratory symptoms and the enlarged hard spleen of trench fever are valuable differential criteria in such cases The typhoidal type is differentiated from true typhoid by the negative Widal reaction and by the almost constant presence of mild to moderate leukocytosis rather than leukopenia In typhoid typhus and dengue fever the onset is more gradual than in trench fever and the rash usually appears several days later Spirochetal relapsing fever and malaria may be excluded by examination of the blood for the specific etiological agents In cases of the chronic type of trench fever with tachycardia fatigue loss of weight and symptoms of neurasthenia the diagnosis may be most difficult It is theoretically possible to establish strong presumptive evidence of trench fever by feeding carefully controlled lice on such patients and finding that they acquire *Rickettsia wolhynica*

Treatment No reliable information is available concerning the value of chloramphenicol and the tetracyclines in trench fever Pain and discomfort should when ever possible be controlled by such drugs as acetylsalicylic acid and phenacetin rather than by opiates Codeine is useful in severe pain Insomnia can usually be controlled by hypnotics The patient should remain in bed under the best available hygienic and dietary conditions for a week or more after complete cessation of subjective and objective evidence of infection He should be kept under observation for several months and returned to bed at the first sign of relapse

Prophylaxis Prevention of the disease is largely a question of efficient delousing by the chemical techniques developed during World War II (see Typhus Fever page 93) Destruction of the infective agent on clothing contaminated by louse excreta is also of primary importance Autoclaving is probably the most satisfactory method Disinfection of urine and sputum may be carried out by chemical methods or by heat Louse proof garments and rubber gloves should be worn by those attending patients or handling clothing Trench fever patients are best treated in separate wards

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BACTERIAL DISEASES

Pneumonia

Pneumococcal Pneumonia

Definition Pneumococcal pneumonia is an acute bacterial infection of the lungs caused by pneumococcus and characterized clinically by an abrupt onset with chills fever chest pain cough and bloody sputum

History Although pneumonia was known to Hippocrates its usual cause was not learned until late in the nineteenth century Pneumococcus was first isolated from normal saliva in 1881 by Pasteur and by Sternberg Several years later its causative role in pneumonia was demonstrated independently by Frankel and Weichselbaum Identification of different serological types of pneumococci which began with the studies of Neufeld in Germany and Dochez in this country led eventually to serum therapy and to the highly significant observations of Avery Enders Heidelberger and Goebels concerning the chemical nature of the capsular antigen and its relation to pathogenicity In 1928 Griffith demonstrated that pneumococci of one type may be transformed into pneumococcal cells of another type This remarkable transforming reaction the epidemiological and genetic implications of which are of great importance has been shown by Avery and his collaborators to depend upon a highly polymerized desoxyribonucleic acid of the bacterial cell Present concepts of the pathogenesis of pneumococcal pneumonia derive from the systematic histological investigations of Robertson and Loeschcke The seriousness of the disease in man was drastically modified by the advent of sulfonamide therapy in the late 1930's and more recently treatment has been further improved by the introduction of penicillin and other antimicrobial drugs

Bacteriology and Immunology More than 95 per cent of all primary bacterial pneumonias are caused by pneumococci The somatic portion of the lancet shaped pneumococcal cell is gram positive In its virulent form pneumococcus has an outer capsule consisting of a loosely packed gel containing a high molecular polysaccharide polymer which is specific for each serological type In addition to the type specific capsular antigen there is in the somatic portion a species specific carbohydrate known as the "C" substance A nontype specific protein antigen can also be demonstrated in the somatic portion of the cell and recently Austrian and MacLeod have identified a type specific protein analogous to the M substance of beta hemolytic streptococci The capsule of pneumococcus acts as an armor against phagocytic cells and thus contributes significantly to the pathogenicity of the organism Pneumococcal variants having no capsules (rough or R strains) are essentially avirulent Antibody to the type specific carbohydrate promotes phagocytosis by combining with the highly polymerized polysaccharide of the capsular gel Antibodies to the other antigens appear to have relatively little effect upon the invasive properties of the organism The pneumococcal cell also produces hyaluronidase a pneumolysin which causes hemolysis in blood agar and autolytic ferments which in time destroy the gram complex and eventually cause dissolution of the cell itself

Pneumococci can be grown on a variety of bacteriological media Blood agar and beef infusion broth containing 0 5 per cent dextrose and 5 to 10 per cent blood or serum are the mediums most commonly used The *pH* of the medium should be approximately 7 5 In a suitable broth the organism grows rapidly and on blood agar virulent (smooth S) strains form circular glistening dome shaped colonies which are alpha hemolytic Because of the great quantity of capsular polysaccharide formed by type III pneumococcus its colonies are more mucoid and usually about twice as large (2 mm in diameter) as those of other types Unlike the alpha hemolytic streptococcus pneumococcus is soluble in bile sodium desoxycholate and other surface active agents is highly sensitive to optochin and is mouse virulent Most strains are virulent for mice rats rabbits dogs and monkeys as well as for man

The extraordinary virulence of pneumococci for mice is made use of in isolating the organisms from sputum The technique usually used consists in injecting intra

pain is most apt to persist in the chronic stage of the disease Abdominal pain and tenderness probably of muscular origin are usually bilateral and more pronounced on gentle than on firm pressure This fact together with the palpable spleen rash and generalized pain and tenderness usually serves to differentiate the condition from appendicitis

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toward the pharynx (at a rate of 1 to 3 cm per hour) (4) the cough reflex which serves to propel the mucus out of the lower tract (5) the lymphatics which drain the terminal bronchi and bronchioles and (6) the mononuclear phagocytes (dust cells) which are ever present in the normal alveoli In addition the alveoli themselves are relatively dry and thus offer a poor medium for growth to the few bacteria that succeed in reaching them Only when the defense barriers of the normal respiratory tract are disturbed does acute bacterial pneumonia result

The thesis that bacterial pneumonia frequently results from aspiration of infected secretions from the upper respiratory tract is strongly supported by both experimental and clinical observations Rats infected with pneumococci in the nasopharynx regularly exhibit pulmonary lesions only when subjected to experimental procedures involving chilling of the body anesthesia administration of morphine and alcoholic intoxication all of which are common predisposing factors in human pneumonia and have been shown in the experimental animal to slow the epiglottal reflex and thus to facilitate aspiration Experimental pneumonia can best be produced by intrabronchial inoculation of organisms suspended in mixtures of gastric mucin or starch having viscosities similar to that of mucus Viral infection of the upper respiratory tract in man usually precedes the onset of acute bacterial pneumonia by several days Not only is the volume of secretion from the nasopharynx greater than normal during viral infections such as the common cold but also the number of pathogenic microorganisms in the secretions is significantly increased Thus the stage is set for aspiration of infected mucus That such aspiration often occurs at the onset of human pneumonia is suggested by the usual sites of initial involvement of the lung The earliest lesions of bacterial pneumonia usually appear in those parts of the lungs into which aspirated fluid is most likely to drain Whereas most air borne bacteria are caught on the sticky surfaces of the bronchial tree and never reach the alveoli organisms contained in thin nasopharyngeal secretions are readily carried into the alveoli by the liquid mucus The latter like Lipiodol cannot all be ejected by ciliary action and much of it penetrates to the farthest reaches of the bronchial tree where it establishes the initial focus of infection

Other factors known to predispose patients to acute bacterial pneumonia include exposure to noxious gases and anesthetics cardiac failure influenzal virus infection of lungs trauma to the thorax and pulmonary stasis resulting from prolonged bed rest A feature common to all these conditions is the accumulation of fluid in the alveoli Harford has shown that the dry lungs of normal mice are able to rid themselves of large numbers of inspired bacteria whereas lungs containing fluid are readily infected This observation suggests that pulmonary edema by providing a suitable culture medium for the bacteria may facilitate the establishment of active infection within the alveoli

Early Lesion Once the infection has gained a foothold within the alveoli the lesion evolves in a characteristic manner The first response of the lung to bacterial invasion is an outpouring of edema fluid into the alveoli This serous fluid not only serves as a suitable culture medium for the organisms but also floats them into new alveoli through the pores of Cohn and terminal bronchioles (Fig 20 *a*) Centrifugal spread of the alveolar fluid is enhanced by motion of the pulmonary parenchyma caused by respiration and cough After the outpouring of edema fluid polymorphonuclear leukocytes and some erythrocytes accumulate in the infected alveoli first in small numbers (Fig 20 *b*) but later in such quantities as to fill each alveolus and thus render the area completely consolidated (Fig 20 *c*) Once the infected alveoli become crowded with leukocytes phagocytosis of bacteria takes place and the invading organisms are destroyed Macrophages appear in the exudate and resolution begins only after most of the organisms have been ingested The macrophages which accomplish the final clearing of cellular debris from the resolving lesion appear to be derived both from monocytes of the blood and from the septal cells of the alveolar walls which become characteristically thickened during the process of resolution (Fig 20 *d*)

Spreading Lesion These stages in the inflammatory reaction account for the distinguishing histological features of the spreading pneumonic lesion In the outermost portion there appears an edema zone in which the alveoli are filled with acellular serous fluid containing many bacteria Inside the edema zone a second zone may be identified in which there are signs of early consolidation with leukocytes in most of the alveoli Here phagocytosis is often noted Still more centrally a third transition to a zone of advanced consolidation is noted where the alveoli are packed with cells and

peritoneally 0 5 cc of sputum previously emulsified by having been drawn repeatedly into a tuberculin syringe When virulent pneumococci are present the mouse dies within forty eight hours and a pure culture of the organism can be isolated from the heart s blood Since other bacteria in the sputum do not ordinarily produce fatal infections in mice the animal serves as a convenient and highly sensitive differential culture medium for the isolation of pneumococci The mouse inoculation technique however cannot be relied upon in recovering type XIV pneumococcus for this organism the capsular polysaccharide of which is immunologically related to blood group A substance is not mouse virulent

More than seventy five different serological types of pneumococci have been identified Typing may be done by agglutination tests with specific antiserums or by the quellung test The latter is based upon the characteristic capsular "swelling" (*quellung*) caused by homologous type specific antibody Tests used for the identification of type specific antibody in serums and other body fluids include in addition to the agglutination and quellung methods mouse protection tests precipitin reactions and opsonocytophagic and bactericidal tests

Antibody usually appears in the blood of patients with pneumococcal pneumonia between the fifth and tenth days of the disease The presence of a significant quantity of antibody in the blood can be demonstrated by the cutaneous reaction resulting from the intracutaneous injection of homologous capsular antigen (Francis skin test) In some untreated patients the appearance of circulating antibody may coincide with recovery but in others no relation can be demonstrated between the crisis and the existence of humoral immunity In severe pneumococcal infections specific polysaccharide which has diffused away from the multiplying bacteria can often be identified by precipitin test in the urine and sometimes can even be detected in the blood Patients frequently continue to excrete the capsular carbohydrate in the urine for days and even weeks after recovery

Epidemiology Pneumococcal pneumonia may occur at any season but is most common during the winter and early spring when respiratory infections in general are most prevalent The high incidence of the disease in winter and spring is undoubtedly due to the fact that acute bacterial pneumonia is usually secondary to injury of the respiratory mucosa by viral infections such as influenza and the common cold

The types of pneumococci that most commonly cause pneumonia in adults are types I III VII II VIII IV XI X XIX and XIV in the order listed Together these ten types account for three quarters of all cases Type XIV is particularly common in childhood infections Other types are occasionally isolated from pneumonic sputum but their comparative rarity suggests that they are of less virulence for man than the more commonly encountered types

Pneumococci particularly of the higher types are frequently present in the respiratory tracts of normal subjects Ordinarily the prevalence of carriers of highly pathogenic types such as I and II is relatively low except for type III which is a common inhabitant of the normal pharynx Nevertheless there is evidence that normal carriers play a more important role in the dissemination of infective types than do patients ill with pneumonia Occasionally in relatively closed communities high carrier rates of pathogenic types are encountered In such circumstances the occurrence of widespread viral disease of the respiratory tract may result in an epidemic of pneumococcal pneumonia Except for these rare epidemics most of which occur in hospitals or custodial institutions the disease is sporadic

Pneumococcal pneumonia is slightly more common in Negroes than in whites and is particularly frequent among workers in steel mills and coal mines It may occur at any age but is of highest incidence in the second third and fourth decades The ratio of male to female patients is approximately three to two the difference probably being due to occupational factors involving frequency of exposure

Pathogenesis and Morbid Anatomy The lung is the only major viscus of the body exposed to the air Since the atmosphere particularly in congested places contains many bacteria it is remarkable that pneumonia is not an almost universal disease The failure of normal subjects to acquire acute bacterial pneumonia as an air borne infection is due to the extraordinarily efficient defense barriers of the lower respiratory tract These defenses include (1) the epiglottis reflex which prevents gross aspiration of infected secretions from the pharynx (2) the sticky mucus which lines the bronchial tree and to which air borne organisms adhere (3) the cilia of the respiratory epithelium which keep the infected mucus moving constantly upward

where beginning resolution may be evident In the central zone of advanced consolidation fibrin is often noted in the alveolar exudate the large fibrinogen molecules having passed through the injured walls of the alveolar capillaries along with erythrocytes

From the foregoing description it is clear that all stages of inflammation can be found in a spreading lesion In the most recently invaded areas at the periphery edema and hemorrhage predominate causing red hepatization " whereas in the older more central parts of the lesion dense consolidation with leukocytes accounts for the characteristic color of "gray hepatization Only if the infection has stopped spreading hours before necropsy will the entire lesion be in the stage of gray hepatization " Thus the spread of pneumococcal pneumonia may be likened to that of a grass fire where the flames having spread centrifugally are concentrated at the periphery leaving behind a charred and burned-out center

Not all pneumococcal pneumonia causes lobar consolidation Less malignant lesions may be patchy in distribution and concentrated particularly about the bronchi Since a clear-cut distinction between pneumococcal bronchopneumonia and lobar pneumonia cannot always be made even by the pathologist and since management of the two conditions is essentially the same it is rarely important for the clinician to differentiate them The etiology rather than the anatomy of the lesion determines therapy

Interlobar Spread If the pneumonic process has involved all the parenchyma of a single lobe its spread may be stopped by the pleural boundaries of the lobe and spontaneous recovery may then ensue Often however the infection spreads to other lobes of the lungs Interlobar spread has been shown in experimental pneumonia to result from the flow of infected edema fluid (Fig 20 e) from bronchi of the involved lung into the bronchial tree of a new lobe Spread to a given lobe may be brought about by suspending the infected animal in such a way that gravity will carry the bronchial fluid into the desired lobe It may be assumed that a similar mechanism operates in human patients with multilobar lesions The fact that the commonest spread in human pneumonia is from one lower lobe to another is in keeping with the assumption that organisms are carried to the new lobe by infected bronchial fluid the flow of which is influenced by cough respiration and the force of gravity

Bacteremia Bacteremia frequently occurs during the course of pneumococcal pneumonia particularly when the infection is fulminating The fact that organisms appear in the thoracic duct in experimental pneumonia before they appear in the systemic circulation suggests that many of the organisms reach the blood stream via the lymphatics It is well known that particles introduced experimentally into the alveoli are cleared primarily by lymphatic drainage At least some of the bacteria in the spreading lesion appear to be removed from the lung by a similar mechanism Their presence in regional mediastinal lymph nodes during experimental pneumonia has been repeatedly demonstrated Whether bacteria gain access to the blood stream by penetrating the alveolar capillaries directly is not known

Invasion of Pleura and Pericardium The exact mechanism whereby pneumococci invade the pleura or pericardium is also unknown Since the lymphatics at the periphery of the lung drain outward toward the pleura it is possible that pleural invasion results from lymphangitic spread On the other hand it is also possible that organisms are carried through the visceral pleura along with edema fluid which accumulates in infected subpleural alveoli When infection of a pleural or pericardial cavity occurs there results an outpouring of serous fluid followed by the deposit of fibrin Later leukocytes accumulate in the infected cavity and if infection persists a purulent focus results The pus in such cavities is at first thin but later becomes thick and stringy as a result not only of fibrin formation but also of the precipitation of desoxyribonucleic acid derived from the nuclei of disintegrating leukocytes Finally the thick fibrinous pus becomes walled off forming loculated foci of chronic suppuration

Similar purulent foci may occur in the meninges or joints probably as a result of hematogenous metastasis Acute vegetations on the endocardium of the heart valves are sometimes encountered and acute splenic tumor indicative of systemic infection is a common finding in fatal cases observed at necropsy Degeneration of renal tubules is also occasionally noted and since identical changes can be produced in the kidneys of laboratory animals by repeated injections of killed pneumococci the lesions are assumed to be of pneumococcal origin

Mechanism of Recovery *Surface Phagocytosis* Because of the antiphagocytic properties of their capsules virulent fully en



FIG 20 *a* Pneumococci in edema filled alveoli at margin of spreading pneumonic lesion (× 800)
b Beginning stage of polymorphonuclear exudation in zone of early consolidation Note leukocytes in alveolar capillaries some in process of diapedesis (× 800)
c Leukocytic exudate (still predominantly polymorphonuclear) in inner zone of advanced consolidation Pneumococci have been phagocyted and destroyed (× 800)
d Alveolar macrophage reaction characteristic of late stage of resolution (× 800)
e Pneumococci in edema fluid contained within lumen of a large bronchus Such infected bronchial fluid causes spread of pneumonia to other lobes of the lungs (× 1250)
f i *Surface phagocytosis of encapsulated microorganisms in formalin fixed rat lung (× 1250)* Bacteria shown in these photomicrographs are Friedlander s bacilli but same results have been obtained with pneumococci
f Polymorphonuclear leukocyte is seen approaching bacteria near alveolar wall Time 12 30
g Leukocyte has reached alveolar wall and is about to trap organisms against the tissue surface Time 12 31
h Cell has trapped some of the encapsulated bacteria against the wall and is in the process of phagocyting them Time 12 32
i Having ingested several of the organisms the leukocyte is moving up the alveolar wall Time 12 35
(Photomicrographs from studies on experimental pneumonia W B Wood *et al* J Exper Med Vol 73 and Smith and Wood *ibid* Vol 86)

layer" which interferes with surface phagocytosis and accounts at least in part for its extraordinary pathogenicity Type III pneumococci may accumulate in huge numbers in infected alveoli and on occasion cause necrosis not only of leukocytes but also of the alveolar walls If the necrosis is sufficiently widespread chronic lung abscesses result

Suppurative Extrapulmonary Foci Suppurative pneumococcal lesions which usually occur in such extrapulmonary sites as the pleura pericardium mastoids or accessory sinuses resolve much less readily even with intensive chemotherapy than does uncomplicated pneumococcal pneumonia In such areas of suppuration phagocytosis is relatively inefficient first because of the fluid present in the lesion secondly because of the absence of such extensive tissue surfaces as are afforded by the alveoli of the lung and thirdly because many if not most of the leukocytes in the exudate are nonviable In addition chemotherapeutic agents administered systemically probably do not penetrate subacute or chronic suppurating lesions as readily as they do areas of acute pneumonia Even when a drug such as penicillin reaches the organisms in a purulent focus it may not necessarily destroy them Pneumococci do not multiply rapidly in pus of long standing and it is well known that resting" bacteria are not susceptible to the antibacterial action of penicillin Thus it is not surprising that clinical experience has demonstrated that purulent pneumococcal infections such as an empyema respond satisfactorily only when chemotherapy is combined with some form of drainage which removes the bulk of the necrotic exudate

Symptoms Victims of pneumococcal pneumonia are often seriously ill when first seen The degree of prostration may be such that an adequate history can be obtained only from the family or some other close associate of the patient The story of a *mild nasopharyngitis* preceding by several days the onset of major symptoms is frequently elicited by careful questioning The first distressing symptom is usually a *shaking chill* lasting for several minutes to a half hour More than 80 per cent of patients with pneumococcal pneumonia experience one or more chills during the earliest stages of the disease The initial rigor is often so violent as to cause the bed to shake and the patient s teeth to chatter It is followed in about one case in three by vomiting The exact cause of the initial chill is not known but it usually coincides with bacterial invasion of the lung and marks the onset of fever Several chills may occur at the start of pneumococcal pneumonia but repeated attacks of rigor late in the disease suggest an extrapulmonary complication such as endocarditis or empyema

Chest Pain In approximately 70 per cent of cases severe chest pain occurs at the onset and may even precede the rigor The pain which is "stabbing" in character and is exaggerated by cough and respiration is caused by inflammation of the pleura resulting from the characteristically peripheral location of the initial lesion There may be local tenderness in the chest wall at the site of the pleurisy When the diaphragmatic surfaces of the pleura are affected the pain is referred either to the corresponding side of the abdomen or to the shoulder depending upon whether the peripheral (intercostal innervation) or central (phrenic innervation) part of the diaphragm is involved The patient may gain some relief from the knife like pain by lying on the affected side thereby partially splinting that half of the thorax

Cough may be absent at the onset but usually is a prominent symptom during the course of the disease Stimulation of the cough reflex results from irritation of the lower respiratory tract and from accumulation of mucus and exudate within the bronchial tree Approximately 75 per cent of patients raise diffusely bloody or "rusty" sputum in contrast to "blood streaked" sputum The thorough mixing of the blood and mucus appears to be due to the fact that bleeding occurs directly into the alveolar exudate and thus constitutes an integral part of the inflammatory response to the infection When the sputum is particularly sticky or jelly like type III pneumococcus or Friedlander s bacillus should be suspected as the cause of the pneumonia since both these organisms produce during growth an inordinate amount of capsular polysaccharide which causes the exudate to be highly viscous

Fever and *toxicity* are constant features of the disease the temperature usually ranging between 103 and 106 F During the febrile period complaints of malaise weakness myalgia and general prostration are extremely common

Physical Signs Since pneumococcal pneumonia may ocasionally progress with great rapidly and the general condition of the patient may deteriorate alarmingly within

capsulated pneumococci are resistant to phagocytosis when suspended in a fluid medium as in ordinary opsonocytophagic tests performed in the laboratory Such is not the case however within consolidated lesions *in vivo* where phagocytosis of fully encapsulated bacteria readily occurs This important difference in phagocytic efficiency has been shown to be due to the presence in tissues of suitable surfaces against which the leukocytes are able to trap the encapsulated organisms and thus ingest them without the aid of opsonizing antibody (see Fig 20 p 116) The efficiency of this surface phagocytosis which operates also within the interstices of fibrin clots depends in large measure upon the amount of fluid present in the lesion In the outer edema zone where fluid is abundant and leukocytes relatively scarce little phagocytosis occurs In areas of more advanced consolidation however where actively motile leukocytes are packed closely together the bacteria are not only effectively trapped against tissue surfaces and fibrin strands within the exudate but are also caught between the surfaces of the phagocytic cells themselves and are thus ingested This efficient mechanism of natural defense operating in the absence of immune bodies explains the prompt destruction of bacteria which is characteristic of the central portions of even the spreading pneumonic lesion Studies on experimental bacteremia have also shown that surface phagocytosis plays an important role in disposing of pneumococci which have invaded the blood stream

Likewise when spread of the lesion is controlled by antimicrobial drugs such as penicillin surface phagocytosis promptly disposes of the bacteria that are not destroyed outright by the drug or by autolysis Consequently it is not surprising that with adequate chemotherapy experimental pneumococcal lesions may clear completely and patients with pneumococcal pneumonia may experience dramatic defervescence many hours before opsonizing immune bodies can be detected in either the serum or the lesion When a patient is treated sufficiently late in the course of the disease antibody may be present in the serum and may then contribute to recovery by accelerating phagocytosis

Macrophage Reaction The exact role of the macrophage reaction in the recovery process is not entirely clear Because the appearance of macrophages in the alveolar exudate coincides in general with the disappearance of organisms from the lesion it has long been assumed that these large mononuclear phagocytes take an active part in destroying the bacteria and in the final analysis tip the scales in favor of the cellular defenses of the host Studies relating to experimental lymphadenitis cast some doubt upon this assumption The macrophage reaction in a regional lymph node draining an area of active infection can be artificially initiated at any stage of the nodal inflammation by merely cutting the afferent lymph vessels bringing bacteria to the node Thus it appears that macrophages accumulate in the exudate only when the active stimulus of direct bacterial invasion has been eliminated If this interpretation is correct the polymorphonuclear leukocytes may be looked upon as the "shock troops that play the major role in controlling the infection whereas the macrophages serve primarily to remove the particulate debris from the resolving exudate and thus promote clearing of the lesion

Resolution One of the most remarkable features of pneumococcal pneumonia is the completeness with which it resolves Even when several lobes are completely consolidated at the height of the illness recovery usually results in restoration of the entire pulmonary parenchyma to its normal state within a few weeks Not all the processes that take part in this dramatic resolution have been identified but they appear to include (*a*) the action of cytolytic ferments upon disintegrating leukocytes (*b*) increased acidity of the exudate (*c*) transport of cells from the lesion via lymphatics and (*d*) phagocytosis and digestion of cellular debris by macrophages The rarity with which tissue necrosis occurs in pneumococcal pneumonia despite the violence of the inflammatory response appears to account for the completeness of the healing Occasionally recovery proceeds more slowly than usual and leads to delayed resolution The factors responsible for delaying the removal of exudate from the lesion in such cases are not known In rare instances as the result of irreversible damage to the pulmonary parenchyma resolution fails to take place altogether and the lesion becomes the site of intense fibroblastic activity which leads to the permanent scarring of organized pneumonia"

Although resolution is usually complete in pneumococcal pneumonia infection with type III pneumococcus may occasionally lead to pulmonary suppuration This particular type of pneumococcus in its most virulent form has a large capsular "slime

parietal pleura over the outer part of the diaphragm The right upper quadrant should always be carefully examined for signs of enlargement or tenderness of the liver resulting from congestive heart failure

In addition to edema from heart failure the most important physical signs encountered in the extremities are those of phlebothrombosis Since pulmonary infarction may closely resemble acute bacterial pneumonia it is of the utmost importance to look for evidence of venous thrombosis in the legs

The neurological examination is rarely

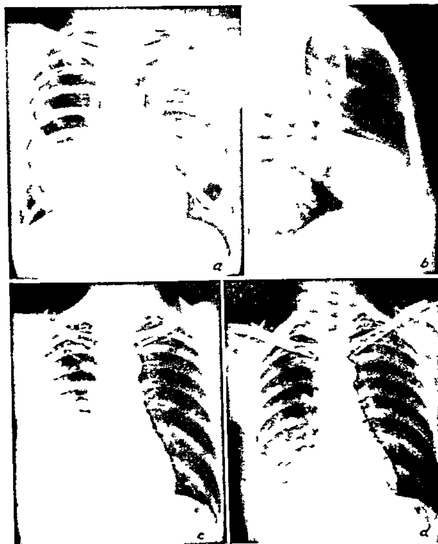


FIG 21 *a* Postero-anterior roentgenogram of chest of fifty year-old man with pneumococcal type VI pneumonia of five days duration Note narrowed intercostal spaces on right and increased density in right lower lung field Such a pulmonary shadow might be due to pneumonia in either the middle (anterior) or the lower (posterior) lobe or in both

b Lateral view reveals that consolidation is confined to middle lobe except for a few small patches in the lower The sharpness and density of the upper border of the middle lobe shadow suggest the presence of a pleural effusion in the interlobar fissure between the upper and middle lobes Sterile pleural fluid was obtained from the interlobar space by thoracentesis The patient recovered promptly with penicillin therapy

c Loculated postpneumonic empyema in a forty year-old white man admitted to the Bellevue Hospital New York on the nineteenth day of pneumococcal pneumonia Only 50 ml of thick greenish pus could be removed from the right chest by aspiration Cultures were sterile Pleural loculations are visible in the roentgenogram Ten milliliters of a preparation containing 100 000 units of streptokinase and 25 units of streptodornase were introduced through the thoracentesis needle Twenty four hours later 465 ml of cloudy thin blood tinged fluid were removed

d Roentgenogram taken after the second thoracentesis performed twenty four hours after enzyme treatment Temperature fell to normal and patient made a rapid recovery No further aspirations were necessary

(*c* and *d* from W. S. Tillett *et al*, Ann Surg, *131* 12, 1950)

a few hours it is essential that the initial physical examination be as thorough as possible

The temperature pulse rate and respiratory rate are usually elevated by the time the patient seeks the aid of a physician The temperature should be taken by rectum since oral measurement with the subject breathing rapidly through the mouth is likely to be inaccurate The pulse pressure is characteristically widened as in any high fever and the pulse at the wrist may be collapsing in quality Subnormal blood pressure indicates shock and a poor prognosis

Patients with well established pneumococcal pneumonia appear acutely ill There is moderate to severe respiratory distress The nostrils dilate with each inspiration Paroxysms of hacking cough often productive of bloody or rusty sputum occur during the examination The chest pain which is usually unilateral may be so severe as to interfere with the patient's breathing and coughing in these circumstances grunting expiration results The location of the pain indicates immediately the approximate site of at least part of the lesion The patient occasionally appears apprehensive and may even be delirious

The skin is usually hot and moist with beads of perspiration visible on the face and forehead Cold extremities may indicate impending shock Herpetic blisters are frequently noted about the mouth The lips mucous membranes and nail beds are often cyanotic as a result of blood passing through involved lung The cyanosis may be exaggerated by poor respiratory exchange caused by severe pleural pain Icterus of the sclerae should be carefully looked for because of the prognostic significance of overt jaundice in pneumonia Occasionally petechiae are found in the skin of patients suffering from complicating pneumococcal endocarditis

The ears should always be examined with an otoscope to exclude the presence of active otitis Tenderness over a mastoid process or over an accessory nasal sinus should also be noted The presence of exudate in the pharynx or over the tonsils suggests the possibility of streptococcal pneumonia Definite nuchal rigidity is usually indicative of pneumococcal meningitis a serious and not too infrequent complication of pneumonia The neck veins must be carefully examined to detect the presence of increased venous pressure caused by complicating congestive heart failure Deviation of the trachea constitutes an important sign of either atelectasis (toward the involved side) or pleural effusion (away from the involved side)

Examination of the Chest The thorax must be examined with the utmost care Diminished respiratory excursion or a slight inspiratory lag of one side of the chest often reveals the site of the principal lesion A localized area of tenderness in the chest wall noted during percussion may be one of the earliest signs of pleural invasion The presence of a large pleural effusion sometimes causes a noticeable fullness of intercostal spaces Careful percussion and auscultation do not invariably reveal signs of consolidation In early cases particularly there may be no conclusive physical signs Lesions at a distance from the chest wall are difficult to outline by percussion Breath sounds may be only slightly depressed if normal lung tissue separates the lesion from the large bronchi When consolidation is extensive the typical findings of dullness to percussion bronchial or tubular breath sounds and fine crackling rales are easily elicited except in the presence of complicating bronchial obstruction or extensive pleural effusion A coarse "leathery" friction rub is frequently audible in the region of consolidation

Examination of the heart may be difficult because of loud respiratory sounds Its position and size should be carefully determined by palpation and percussion A later shift in the position of the left cardiac border may indicate any one of the following complications cardiac enlargement from heart failure invasion of the pericardial cavity atelectasis or pleural effusion An apical systolic murmur is frequently heard during high fever and is often of no significance although it may be due to bacterial vegetation Diastolic murmurs on the other hand arising from either the mitral or aortic valve are usually indicative of underlying organic heart disease or complicating pneumococcal endocarditis A pericardial friction rub often constitutes the first sign of spread of the pneumococcal infection to the pericardial cavity Ventricular premature contractions are not uncommon in the presence of any moderate or severe infection

Abdominal Distention Distention of the abdomen is frequently encountered in advanced bacterial pneumonia Its presence is due to paralytic ileus Occasionally the examiner will note rigidity and even tenderness in one or both upper quadrants of the abdomen suggesting a subdiaphragmatic lesion This sign is usually due to referred pain resulting from involvement of the

slight secondary rise in temperature occurs after the crisis and low grade fever may persist during the first few days of recovery Not only does defervescence occur promptly after effective therapy but the patient experiences striking relief of symptoms and exhibits a marked improvement in general appearance Physical signs in the chest also change within a few days coarse sticky rales of resolution replacing the fine crepitant rales and tubular breath sounds of consolidation Complete clearing of the pulmonary lesion may occur within a few days but usually the auscultatory signs of resolution persist for a week or more after defervescence If resolution is not complete within twenty-one days it is arbitrarily classified as delayed The promptness of defervescence and the speed of resolution are in general inversely proportional to the age and extent of the lesion at the time treatment is begun

Crisis marking the start of recovery must be differentiated from the pseudocrisis" occasionally noted at the onset of peripheral vascular collapse or at the time of interlobar spread of the infection Although the temperature may fall precipitously during a pseudocrisis the pulse rate remains elevated and the patient s general condition fails to improve

Relapse may occur in pneumococcal pneumonia particularly when chemotherapy is discontinued too soon If fever tachycardia and other signs of active infection recur while the patient is still receiving intensive penicillin therapy it may usually be assumed that a previously unrecognized purulent complication of the pneumococcal infection (such as empyema) exists that a drug resistant secondary invader has gained a foothold in the lung or that hypersensitivity of the patient to penicillin has caused the development of drug fever

Complications The commonest specific complication of pneumococcal pneumonia is pleurisy with effusion In somewhat less than 10 per cent of cases fluid can be demonstrated in the pleural cavity by either physical or roentgenographic examination Such effusions are usually small and when sterile are rarely of significance They result from inflammation of the pleura overlying the parenchymal lesion of the lung Occasionally they may be of sufficient volume to cause respiratory embarrassment and necessitate thoracentesis Whenever pleural effusion is detected in a patient who has failed to respond promptly to treatment a thoracentesis should be performed in order to determine whether the fluid is infected and is thus in effect an empyema Samples of the fluid obtained should be examined directly with bacterial stains inoculated intraperitoneally into a mouse and cultured both aerobically and anaerobically

Empyema Empyema though less common than sterile pleural effusion is far more serious Before the advent of chemotherapy the incidence of this complication was approximately 5 per cent With the present widespread use of penicillin empyema is much less common (under 2 per cent) Its presence is indicated by continued fever (often irregular) persistent leukocytosis repeated sweats and signs of pleural effusion (Fig 21 c) Localized tenderness is frequently noted in the chest wall overlying the site of the lesion The exudate in the plural cavity may become loculated by thick fibrinous adhesions If it is present in sufficient quantity it may cause fullness of intercostal spaces and a shift of the trachea and mediastinum away from the side of the lesion When the lesion is confined to an interlobar fissure or located in the thoracic "gutter adjacent to the spine it may be detectable only by roentgenographic methods Repeated exploratory thoracenteses may be required to prove the presence of empyema Its detection is of the greatest importance since once discovered it is amenable to proper therapy whereas if left untreated it may eventually drain exteriorly through the chest wall (empyema necessitatis) or rupture into a bronchus and cause a bronchopleural fistula Rarely empyema heals spontaneously causing calcification of the pleura The fluid contained within an empyema cavity is at first thin but soon becomes so thick and stringy that aspiration through a needle is difficult The solid material within the pus is composed not only of fibrin but also of desoxyribonucleic acid derived principally from the nuclei of disintegrating leukocytes Tillett has shown that both these solid components can be dissolved by enzymes (streptokinase and streptodornase) derived from beta hemolytic streptococci As indicated under Treatment this discovery has led to an important advance in therapy The initial sample of exudate obtained by thoracentesis should always be subjected to bacteriological study (see under Pleural Effusion) since identification of the offending organism is essential for proper treatment

Meningitis and Endocarditis Two serious but now comparatively rare complica

abnormal in pneumococcal pneumonia except in the presence of meningitis or brain abscess Digital examination of the rectum may be postponed if the patient is acutely ill but in women a sufficiently complete pelvic examination should be performed to rule out the possibility of an infected abortion which often leads to metastatic bacterial pneumonia

Laboratory Findings *The most important* laboratory findings in pneumococcal pneumonia may be grouped under the following headings

1 *Findings Indicating the Presence of an Acute Infection* As in most acute infections of bacterial etiology the total leukocyte count in pneumococcal pneumonia is elevated and there is a shift to the left" in the differential count the erythrocyte sedimentation rate is also increased The number of leukocytes in the peripheral blood during the active infection usually ranges from 15 000 to 40 000 per cu mm counts above 40 000 are occasionally encountered Leukopenia (with a "shift to the left") is observed in fulminating pneumococcal infections particularly in the presence of bacteremia

2 *Findings Indicating Pulmonary Consolidation* Although the presence and location of the pulmonary lesion can usually be determined by physical examination confirmatory roentgenographic evidence is often helpful Patients seen in the hospital should either be fluoroscoped (on a stretcher if necessary) or subjected to roentgenographic examination Both postero-anterior and lateral views of the chest should be taken The lateral film may be of great value in (*a*) detecting retrocardiac consolidation in the left lower lobe (*b*) indicating whether a lesion visible in the postero anterior view is located anteriorly or posteriorly and thus in what lobe it is situated and (*c*) identifying interlobar accumulations of fluid (Fig 21 *a b*) If the patient is too ill to be subjected to such a complete examination a portable chest film should be taken at the bedside Proper management of pneumococcal pneumonia in the home does not necessarily require roentgenographic examination

3 *Findings Indicating Etiology* Whenever the diagnosis of pneumococcal pneumonia is suspected blood should be drawn for culture Anaerobic (thioglycollate broth) as well as aerobic cultures are recommended since many strains of pneumococci multiply most readily at a reduced oxygen tension A positive blood culture not only affords clear-cut evidence regarding etiology but also gives valuable information concerning prognosis The physician should make a real effort to obtain a suitable specimen of sputum Whenever possible the patient should be made to expectorate mucus raised directly from the bronchial tree secretions from the nasopharynx may be unsatisfactory The specimen should be taken to the laboratory immediately to be cultured inoculated intraperitoneally in a mouse and smeared for Gram stain When typing serums are available direct typing of the sputum should be attempted and if unsuccessful the pneumococci isolated by culture or mouse inoculation should be identified by the quellung technique The practical importance of pneumococcal typing today is limited but is of some value in differential diagnosis as noted below In the days of serum therapy however specific treatment could not be begun until the type of the infecting organism had been determined When no sputum specimen can be obtained from the patient a throat swab may be cultured Although it is not a hazardous procedure lung puncture is now rarely used to determine the etiology of acute bacterial pneumonia

Other laboratory examinations which may be of value in the management of the patient include the measurement of serum sodium and chloride During the acute phase of bacterial pneumonia there may be a profound disturbance in electrolyte metabolism characterized by (*a*) depressed urinary excretion of sodium chloride and (*b*) decrease in the concentration of sodium and chloride in the serum Both these changes appear to be due to transfer of sodium chloride from plasma and extracellular fluid In particularly severe infections hyponatremia and hypochloremia may be associated with "prerenal" azotemia and shock The exact mechanism of the electrolyte disturbance is at present not known

Clinical Course During the course of the disease the patient should be examined carefully once a day More frequent physical examinations may unduly exhaust an acutely ill subject The common complications of pneumococcal pneumonia should be specifically looked for during each examination particularly when fever persists

Defervescence The fever of untreated pneumococcal pneumonia may either terminate abruptly by "crisis" five to ten days after the onset or may gradually subside by lysis When effective antibacterial therapy is used a dramatic crisis often ensues within twenty four hours Sometimes a

uncommon in only moderately severe cases As in any bedridden patient phlebothrombosis may occur during pneumonia Its presence should suggest the possibility that the pulmonary lesion is due to infarction of the lung rather than to primary pneumonia *Herpes labialis* occurs in 5 to 40 per cent of patients with pneumococcal pneumonia and constitutes an essentially benign complication Occasionally the herpetic lesions become secondarily infected causing mild pyoderma

Differential Diagnosis The symptoms and signs of pneumococcal pneumonia are usually so characteristic as to make the diagnosis relatively simple Atypical cases occasionally occur in which a definitive diagnosis cannot be made and in which antimicrobial treatment on suspicion is justified Sometimes the disease is mistaken for less serious forms of respiratory tract infection such as acute tracheobronchitis or "grippe" This error can often be avoided if proper significance is attached to the history of chills bloody sputum and chest pain if the lungs are carefully examined at frequent intervals for signs of pulmonary consolidation and if postero-anterior and lateral roentgenograms are made of the chest

Pneumonia due to organisms other than pneumococcus may at times be difficult to differentiate from pneumococcal pneumonia Only by bacteriological study of the sputum can pneumonia due to Friedlander s bacillus *Staphylococcus aureus* or group A beta hemolytic streptococcus be identified Tuberculous pneumonia rarely causes the acute prostration characteristic of coccal infection *Primary atypical pneumonia* and other viral and rickettsial infections of the lungs such as psittacosis and Q fever do not often cause shaking chills diffusely bloody sputum severe pleural pain or a marked leukocytosis although they may at times be confused with acute bacterial pneumonia (see p 135) Tularemic pneumonia must also be considered When the diagnosis is in doubt repeated examinations of the sputum should be made using both the Gram and Ziehl Neelsen stains Sputum specimens should not only be cultured but should be injected into mice The identification of one of the lower types of pneumococcus (excluding type III) constitutes strong circumstantial evidence in favor of the diagnosis of pneumococcal pneumonia Specific diagnosis of pneumonia is of great practical importance because of therapy Whereas tuberculous tularemic and Friedlander s bacillus pneumonia respond to streptomycin and individual instances of primary atypical pneumonia might be influenced by the tetracycline drugs most other forms of acute pneumonia are best treated with penicillin

Nonpulmonary Bacterial Infections Bacterial infections other than pneumonia must be considered in the differential diagnosis Pleurisy involving the outer part of the diaphragm and resulting from right lower lobe pneumonia often causes referred pain to the right side of the abdomen thus simulating acute appendicitis Subdiaphragmatic abscess arising from perforation of the appendix conversely may simulate pneumonia Acute pyelonephritis with chills fever flank pain and leukocytosis must not be confused with pneumonia the diagnosis is usually established by examination of the urine and by the absence of signs of frank consolidation in the lungs Differentiation of acute pyelonephritis from pneumococcal pneumonia is of primary importance since most urinary tract infections are caused by organisms that are not susceptible to penicillin

Noninfectious Diseases Among the essentially noninfectious processes which must be differentiated from pneumococcal pneumonia are congestive heart failure pulmonary infarction and atelectasis That *congestive heart failure* predisposes to acute bacterial pneumonia has already been emphasized The two conditions not infrequently coexist but occasionally congestive heart failure is mistaken for pneumococcal pneumonia This error is most frequently made in cases with dyspnea cough blood streaked sputum and signs in the chest which simulate those of consolidation but in reality are due to pleural effusion In such cases the absence of high fever and leukocytosis and the presence of distended neck veins and peripheral edema usually suggest the correct diagnosis

Pulmonary infarction on the other hand is more difficult to differentiate from pneumonia The dyspnea pleural pain hemoptysis fever physical signs of pulmonary consolidation roentgenographic findings and leukocytosis are all in keeping with an acute infection of the lungs Not infrequently however the initial symptom is intense pleural pain of explosive onset shaking chills rarely occur there is no preceding history of respiratory infection the fever usually is not high frank hemoptysis is common pulmonary signs when present appear early and the total leukocyte count rarely reaches 20 000 per cu

tions of pneumococcal pneumonia which are often associated with one another are endocarditis and meningitis Eighteen out of nineteen cases of pneumococcal endo carditis described by Ruegsegger were *complicated by the presence of meningitis* Endocardial infection which occurs most commonly on the aortic valve may be sug gested by repeated chills persistent fever and leukocytosis and the presence of a cardiac murmur The diagnosis is estab lished by the identification of embolic phenomena (see Bacterial Endocarditis) and by the demonstration of persistent bac teremia Only rarely does recovery occur without treatment Equally serious is pneu mococcal meningitis resulting from blood *borne metastasis to the meninges* Its presence is indicated by the usual mani festations of meningitis (headache nausea and vomiting stiff neck positive Kernig s sign stupor and so forth) and the diag nosis is established by the demonstration of purulent cerebrospinal fluid containing pneumococci *The meningitis is character* ized by the presence in the pia arachnoid of a heavily infected exudate which may cause subarachnoid block or lead to local ized subarachnoid abscesses Unless vigor ous therapy is instituted promptly the prognosis is hopeless

Pericarditis Like the other complications of pneumococcal pneumonia pericarditis has also become relatively rare since the introduction of potent antimicrobial drugs When the pericardium is invaded the patient usually experiences precordial pain and a leathery friction rub may be heard over the heart Pericardial effusion usually results causing a dampening of the heart sounds If the fluid is sterile the condition is benign unless so large a volume accum ulates as to cause cardiac tamponade Empyema *of the* pericardium on the other hand is a serious complication requiring prompt and vigorous treatment If it is allowed to persist untreated purulent peri carditis may gradually heal but will often lead to pericardial calcification Years later serious constriction of the heart may result from contraction of the healed lesion

Other Specific *Complications* Still rarer specific complications include peritonitis pyogenic arthritis *metastatic* cutaneous ab scesses and nephritis The last of these usually occurs several weeks after the pneu monia the latent period appearing to be similar to that in nephritis following group A streptococcal infection Occasionally the pulmonary lesion of pneumococcal pneu monia fails to resolve even after many weeks and finally becomes replaced by fibrous tissue This complication is termed organized pneumonia and rarely causes serious disability unless accompanied by suppuration

Nonspecific Complications Three non specific complications of importance occur not infrequently during the acute phase of pneumococcal pneumonia paralytic ileus peripheral vascular collapse (shock) and congestive heart failure *Ileus* occurs par ticularly in patients suffering from anoxia and severe toxemia and gives rise to gas eous distention of the abdomen (tym panites) which causes discomfort and of ten increases respiratory embarrassment *Shock* likewise is a complication of severe *toxemia and* indicates a serious prognosis The circulatory disturbance is characterized by hemoconcentration an increased rather than a depressed cardiac output and pe ripheral vasodilatation Whether "toxic myo-carditis" also plays a role is uncertain The skin particularly of the extremities is cold and moist and exhibits a *characteristic* gray cyanosis Peripheral vascular failure when present for a sufficient length of time becomes irreversible and the patient eventually dies in shock despite the fact that the infection in the meantime may have been adequately controlled by chemo therapy *Congestive heart failure* which also occurs not infrequently as a compli cation of severe pneumonia particularly in patients with underlying heart disease must be differentiated from peripheral vas cular collapse for the proper methods of treating the two conditions are different Since congestive heart failure is an impor tant predisposing factor in bacterial pneu monia it is not surprising that they are often associated and obviously both must be treated The diagnosis of congestive heart failure in the presence of pneumonia may at times be difficult but should be considered in any patient with abnormal distention of neck veins peripheral edema an enlarged tender liver elevated venous pressure and a prolonged circulation time Pulmonary signs of congestion may be unreliable particularly if the pneumonia is bilateral

Jaundice the pathogenesis of which ap-pears to be related to increased hemolysis of the erythrocytes in the pneumonic lesion and depressed liver function resulting from anoxia occurs most often in patients who have severe pneumonia and have had a poor diet The presence of prominent icterus usually indicates a poor prognosis although slight hyperbilirubinemia is not

to seven days Not infrequently a secondary rise in temperature occurs after the crisis This elevation is usually low grade and subsides spontaneously within a few hours or at most a few days Such secondary fever must be distinguished from that caused by complications or continued pulmonary infection and can usually be recognized by the fact that it is accompanied neither by symptoms of continued toxicity nor by significant leukocytosis

When a patient fails to respond within forty-eight hours to penicillin therapy three possible explanations should be considered (*a*) that the patient is suffering from a serious complication such as empyema endocarditis or meningitis (*b*) that the primary infection is of nonpneumococcal etiology and is due to an agent that is resistant to the antimicrobial action of penicillin or (*c*) that drug fever has developed as a result of penicillin hypersensitivity Lack of response to penicillin cannot be explained on the basis of a penicillin resistant strain of pneumococcus since such strains are rarely if ever encountered in human pneumonia Occasionally patients will respond initially to treatment only to have unmistakable signs of persistent pneumonia subsequently develop in spite of continued therapy This sequence of events is usually due to the presence of a mixed infection the initial response to treatment resulting from control of penicillin susceptible organisms and the relapse occurring as a result of secondary invasion by penicillin resistant species Immediate institution of combined therapy with streptomycin erythromycin or a tetracycline drug is indicated in all such cases

Toxic reactions to penicillin are rarely of sufficient severity to warrant discontinuation of treatment Urticaria may be bothersome and a combination of symptoms and signs suggesting "serum sickness occasionally occurs Patients with dermatophytosis may experience an exacerbation of the lesions during penicillin therapy

SULFONAMIDES Sulfonamides such as sulfathiazole sulfadiazine and sulfamerazine although effective in the treatment of pneumococcal pneumonia should not be used for the following reasons (1) Penicillin is a more potent antibacterial agent than the sulfonamides it causes more prompt destruction of the bacteria and it is far more effective in controlling purulent complications and (2) toxic reactions to sulfonamides (particularly to sulfathiazole) are significantly more common than to penicillin and include such conditions as toxic nephritis and periarteritis nodosa which may terminate fatally There is no conclusive evidence that combined penicillin sulfonamide therapy is any more effective than treatment with penicillin alone except possibly in the presence of meningitis or in the case of mixed infections involving penicillin resistant organisms In the latter situation other antimicrobial drugs (see above) rather than sulfonamides should be combined with penicillin

ANTISERUM Type specific antiserum is no longer used in the treatment of pneumococcal pneumonia

The TETRACYCLINE DRUGS and CHLORAMPHENICOL may be used in the treatment of acute bacterial pneumonia When the diagnosis of pneumococcal pneumonia is not clearly established it may be advisable to use one of the tetracyclines (0 5 to 1 0 gm by mouth every six hours) because of their broader antibacterial action and their possibly beneficial effect in primary atypical pneumonia Staphylococcal enteritis may result from the use of "broad spectrum antibiotics such as the tetracyclines and if not promptly treated may be fatal Erythromycin is less effective than penicillin or the tetracyclines in pneumococcal pneumonia and should be used (0 3–0 5 gm every six hours) only when the lesion is suspected of harboring penicillin resistant staphylococci

Supportive Treatment Patients suffering from pneumococcal pneumonia should be kept at bed rest and visitors to the sick room should be limited to the immediate family Pleural pain if mild may be treated with codeine sulfate (30 to 60 mg) orally and if severe with subcutaneous morphine sulfate (10 to 15 mg) or an equivalent analgesic such as methadone hydrochloride (5 to 10 mg subcutaneously) A tight chest binder is sometimes helpful in providing something to cough against " Restlessness and insomnia which are most commonly associated with delirium are best controlled by paraldehyde (4 to 12 ml by mouth or 10 to 20 ml in 20 to 30 ml of olive oil by rectum) Dyspnea and cyanosis should be treated with oxygen administered by tent (40 to 60 per cent oxygen) or by nasal catheter (35 to 50 per cent oxygen when gas is delivered at 4 to 7 liters per minute) Oxygen masks are usually unsuitable because of the patient s cough and expectoration

FLUID AND ELECTROLYTES During the acute stage of pneumococcal pneumonia considerable fluid is lost from the body

mm When a pulmonary infarct becomes infected as not infrequently happens differentiation from primary bacterial pneumonia may be extremely difficult Although in such cases the patients should receive antimicrobial treatment as in pneumonia recognition of the infarction is of importance because of the need for anticoagulant therapy

Pulmonary atelectasis resulting from bronchial obstruction not only may simulate pneumonia but often leads to serious *infection of the lung if the bronchial ob*struction is not relieved Aspiration of mucus during or after surgical anesthesia is a common cause of atelectasis Dyspnea cough chest pain splinting of one side of the thorax dullness to percussion and suppressed breath sounds may all suggest primary pneumonia Fever and leukocytosis also are noted when infection is present Since pulmonary atelectasis may be relieved by forced coughing and postural drainage or if necessary by bronchoscopy it is important to differentiate it from primary pneumonia Occasionally sufficient shift of the mediastinum occurs to make the diagnosis obvious Collapse of a segment of the lung may also result from chronic bronchial obstruction due to bronchogenic carcinoma or aortic aneurysm

Even when the diagnosis of pneumococcal pneumonia is established beyond doubt the possibility of a second underlying lesion of the lung must be borne in mind Bronchiectasis may lead to repeated attacks of bacterial pneumonia and often becomes evident only after the pneumonic consolidation has resolved Bronchogenic carcinoma as well as pulmonary tuberculosis must likewise be looked for during the follow up examination

Treatment The treatment of pneumococcal pneumonia may best be discussed under three headings (*a*) antimicrobial therapy (*b*) supportive measures and (*c*) the treatment of complications Before the advent of effective antibacterial therapy supportive treatment was of the greatest importance The introduction first of antipneumococcal serum and later of sulfonamides penicillin and the other antimicrobial drugs has so altered the management of pneumococcal pneumonia that today supportive treatment is rarely crucial and serious complications are only occasionally encountered

Antibacterial Therapy PENICILLIN Penicillin is at present the drug of choice in the treatment of pneumococcal pneumonia Most strains of the organism are extremely susceptible to penicillin and are inhibited in broth culture by concentrations of less than 0 01 unit per ml The effectiveness of antimicrobial treatment is due in part to the natural resistance of the host which accounts for the destruction of a large proportion of the invading bacteria Host resistance which results primarily from the activity of phagocytic cells in the lung when combined with the bacteriostatic and bactericidal effects of drug therapy controls promptly all but the most malignant pneumonia *Even with no treatment at all* approximately seven of every ten patients with pneumococcal pneumonia eventually recover

Conventional penicillin therapy involves the intramuscular administration of 300 000 or 400 000 units two to four times each twenty four hour period depending upon the severity of the infection Treatment should be maintained for at least one week if treatment is discontinued too soon relapse of the infection occurs Since penicillin continues to exert a bacteriostatic effect for several hours after the drug has been removed from the site of infection the interval between injections may be as long as twelve hours provided large enough doses (300 000 to 600 000 units) are given In severe infections however it is safest to give the drug at least every six hours

Penicillin may also be given by mouth When oral penicillin is used it must be prescribed in doses five times as large as those used intramuscularly since only 20 to 30 per cent is absorbed from the gastro intestinal tract and it should not be given just preceding or immediately following a meal Slowly absorbed (depot) penicillin in the form of the procaine salt may be injected intramuscularly in doses of 300 000 units once or twice a day This form of treatment though convenient to both patient and physician should not be relied upon in severe infections since the blood levels attained are considerably lower than those resulting from multiple injections of aqueous penicillin In the presence of shock aqueous penicillin should be given intravenously

Response to penicillin therapy is usually dramatic Bacteremia when present at the start of treatment clears within a few hours A crisis characterized by rapid defervescence and a striking subsidence of symptoms occurs in less than forty eight hours in approximately 85 per cent of patients The remaining 15 per cent experience a more gradual recovery the temperature falling by lysis over a period of three

longstanding purulent exudates which otherwise would be too thick to aspirate through even the largest thoracentesis needle Loculation also is broken up by the enzymatic débridement" Because of their large molecular dimensions the streptococcal enzymes do not penetrate living cells and therefore are not injurious to tissue or to viable phagocytes The streptokinase and streptodornase are injected directly into the pleural (or pericardial) space in doses of 200 000 to 400 000 units and 50 000 to 100 000 units respectively A mild and transient febrile reaction often occurs within a few hours Several injections may be necessary particularly when the empyema has become loculated By the use of the streptococcal enzymes combined with daily aspiration and the local injection of penicillin prompt and permanent cures of both acute and relatively chronic empyemas have been effected (Fig 21 c d)

The treatment of the remaining two major complications of pneumococcal pneumonia namely meningitis and endocarditis are discussed elsewhere (see Meningitis and Bacterial Endocarditis)

Prognosis The case fatality rate in untreated pneumococcal pneumonia ranges from 20 to 40 per cent The widespread use of sulfonamide drugs in the late 1930s resulted in a lowering of the fatality rate among treated patients to approximately 10 per cent Penicillin therapy has lowered the rate still further At present approximately 95 per cent of patients with pneumococcal pneumonia recover when properly treated with penicillin

The prognosis in pneumococcal pneumonia is influenced adversely by each of the following (1) old age (and also infancy) (2) late treatment (3) infection with certain types of pneumococci (particularly types II and III) (4) involvement of more than one lobe of the lung (5) leukopenia (6) bacteremia (7) jaundice (8) the presence of complications (notably shock and meningitis) (9) pregnancy (particularly in the third trimester) (10) the presence of other disease (*i e* heart disease cirrhosis of liver and so forth) (11) alcoholism Through a consideration of these factors a rough estimate may be made of the severity of the infection in each individual case and therapy may be modified accordingly

Prevention Since pneumococcal pneumonia is not highly contagious and since it responds promptly to early therapy prophylaxis constitutes less of a problem than it does in many other infectious diseases It is estimated that only one in every 500 persons of all ages in the United States may be expected to contract the disease in any one year In certain closed communities however and in areas where the pneumococcal carrier rate is particularly high epidemics occasionally occur Under such conditions immunization with pneumococcal polysaccharide may be indicated During World War II the effectiveness of polyvalent pneumococcal vaccine in preventing pneumonia and in lowering the pneumococcal carrier rate was clearly demonstrated in a controlled experiment on Army personnel Although immunization may prove to be of value in military medicine its application to the general population is not indicated because the *incidence* of the disease in ordinary circumstances is too low to justify vaccination Likewise the use of methods of "air sterilization by ultraviolet radiation and by aerosols is of limited applicability

Although pneumococcal pneumonia can undoubtedly be prevented (or at least aborted) in many patients by the intensive treatment of every upper respiratory tract infection with antimicrobial drugs their indiscriminate use for this purpose should be avoided The possible inconvenience to the patient of hypersensitivity reactions and the theoretical danger of producing drug resistant strains of bacteria outweigh the advantages to be gained in preventing such a relatively uncommon and readily treatable disease as pneumococcal pneumonia Such chemoprophylaxis during outbreaks of epidemic influenza on the other hand might conceivably be indicated

Isolation Procedures Ideally every patient with pneumococcal pneumonia should be placed in respiratory isolation all attendants and visitors being required to wear masks when in the patient's room The isolation precautions should be enforced until the patient has been afebrile for several days The cross infection rate in pneumococcal pneumonia is low and patients receiving chemotherapy are probably not highly infectious Hence isolation rules are often disregarded without apparent ill effect The danger of cross infection in a general hospital particularly among patients with congestive heart failure pulmonary edema or other severe debilitating diseases may be greater than in the general population

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chiefly through the skin as the result of high fever Dehydration may develop rapidly and if severe may become a contributing factor in the development of shock Most patients require between 3 and 4 liters of fluid a day when the fever is high Because of the loss of salt through the skin and the tendency for the serum sodium to be low during the acute phase of the infection it is advisable to supplement the intake of sodium chloride with 1 per cent salty broth A total daily intake *of 6 to 10 gm of salt is usually sufficient* Intravenous saline may be used if the patient is unable to take fluid by mouth In the presence of congestive heart failure the use of supplementary sodium chloride is contraindicated In the absence of renal disease glycosuria or congestive heart failure the patient s state of hydration may be estimated by the specific gravity of the urine When hydration is adequate the specific gravity should remain below 1 020

DIET Many patients with pneumococcal pneumonia are too ill to tolerate a full diet and should receive only liquids during the height of the fever Fruit juices ginger ale and soups are well tolerated After the crisis a regular diet may be prescribed

The patient should be kept in bed until the temperature has been normal for several days and should be observed closely until the pneumonic lesion has resolved As already emphasized all patients should be subjected to a follow up roentgenographic examination three to four weeks after recovery

Treatment of Complications SHOCK Patients with peripheral vascular collapse (shock) resulting from severe pneumococcal pneumonia usually respond poorly to the accepted forms of antishock therapy The prognosis is almost invariably grave when this complication develops Oxygen therapy should be begun immediately even if cyanosis is absent Norepinephrine is at present the best drug available for combating peripheral vascular collapse It should be given continuously by intravenous drip in sufficient amounts to maintain the systolic pressure at levels between 100 and 110 Enough norepinephrine (one vial contains 4 mg) must be added to each liter of salt solution so that the hypotension can be controlled by the administration of not more than 2000 to 3000 ml of fluid in twenty four hours Hydrocortisone given intravenously may also be of value (300 mg during the first twenty four hours with daily dose decreased thereafter to 50 or 100 mg) These measures should be used only with the greatest caution if signs of congestive heart failure are also present The treatment of congestive heart failure in patients with pneumococcal pneumonia is essentially the same as the treatment of heart failure under other conditions (see The Treatment of Congestive Heart Failure)

ABDOMINAL DISTENTION Abdominal distention (paralytic ileus) is best managed by the use of daily enemas the insertion of a rectal tube the administration of oxygen *the application of heat to the abdomen* (warm turpentine stupes) and repeated hypodermic injections of prostigmine methylsulfate (0 5 mg) The prostigmine injections should be repeated every hour until a definite effect is obtained subsequent doses should be spaced at intervals of two to four hours and maintained as long as is necessary

Delirium may sometimes be difficult to control particularly in patients with a history of chronic alcoholism The use of 30 to 90 ml of whisky per day may quiet alcoholic patients during the acute phase of the disease The safest hypnotic to use is paraldehyde A restraining net over the bed is often required to prevent the patient from climbing out of bed and injuring himself

EMPYEMA AND PERICARDITIS The treatment of empyema and of purulent pericarditis until recently has always been surgical During World War I Graham demonstrated that open thoracotomy must always be delayed until the pus aspirated from the chest is relatively thick and the area of infection is sufficiently well walled off to prevent marked shift of the mediastinum Since the advent of penicillin cases *of both empyema and pericarditis have* been successfully treated by repeated aspiration and injection of aqueous penicillin (50 000 to 200 000 units daily) through a thoracentesis needle More recently Tillett and his co workers have demonstrated that the treatment of empyema without surgical drainage is greatly facilitated by the use of two enzyme preparations obtained from filtrates of beta hemolytic streptococci The first of these enzymes *streptokinase* activates the fibrinolytic system in plasma and thereby causes lysis of the fibrin contained in purulent exudates The second enzyme known as *streptodornase* (abbreviation for *streptococcal desoxyribonuclease*) brings about depolymerization of the desoxyribo nucleoprotein By lysing both the fibrin and the nucleoprotein the streptococcal enzymes cause a dramatic liquefaction of

symptoms of catarrhal inflammation of the upper respiratory tract and a more or less severe febrile reaction accompanied by malaise headache and muscular aching

The mortality rate in epidemic influenza is low and secondary bacterial pneumonia is relatively uncommon During recent years cases of associated staphylococcal pneumonia have occurred in some outbreaks and this was especially true in the epidemic caused by the Asian variety of type A influenza virus which occurred during the fall and winter of 1957–1958 The incidence of pulmonary involvement attributable to the virus itself has varied considerably in different epidemics but in the majority it has been small However it should be remembered that the virus alone in the proper circumstances can cause a fulminating and fatal pneumonia

For further information on influenzal pneumonia see the section on Influenza (p 10)

Q FEVER PNEUMONIA

Q fever has been found to have virtually a world wide distribution and serological surveys have revealed evidence of its presence in nearly all parts of the United States The etiological agent is a filter passing species of rickettsia *Coxiella burnetii* Although the infection is essentially systemic it is usually but not always accompanied by a more or less extensive pneumonitis Cases with pulmonary involvement present a clinical picture and roentgenographic findings indistinguishable from those of primary atypical pneumonia The disease responds readily to treatment with a tetracycline drug

For further information on Q fever see the section on Rickettsial Diseases (p 109)

PNEUMONIA IN SMALLPOX

Pulmonary lesions occur frequently in smallpox Variola virus produces a specific bronchopneumonia with characteristic inclusion bodies in many of the affected cells The pneumonia may be a serious complication since there is a pronounced predisposition to secondary invasion by pyogenic bacteria particularly staphylococci

PNEUMONIA IN CHICKENPOX

A diffuse and sometimes fatal bronchopneumonia occurs occasionally in chickenpox especially among adult patients (see Varicella p 28) In a number of autopsied cases the absence of bacteria and the character of the pathological findings have indicated that the pulmonary lesions may be caused solely by the virus The administration of cortisone in severe cases has proved to be beneficial and even life saving in some instances

PNEUMONIA IN MEASLES

Bronchopneumonia occurs frequently in measles The pneumonitis resembles other forms of viral pneumonia and is often caused solely by a specific reaction to the measles virus Superimposed bacterial infection is common however and accounts for the majority of the severe or fatal cases *Streptococcus haemolyticus* *Staphylococcus aureus* and *Hemophilus influenzae* are the usual secondary invaders In recent years the mortality rate from measles pneumonia has been markedly reduced by treatment with antimicrobial drugs Penicillin is the agent of choice in most instances

PNEUMONIA IN LYMPHOCYTIC CHORIOMENINGITIS

Lymphocytic choriomeningitis is caused by a specific viral agent The disease in man is usually characterized as an acute aseptic meningitis but occasionally a grippelike syndrome is produced without clinical evidence of central nervous system involvement Several cases with pulmonary involvement have also been described and the virus has been isolated from the lung at necropsy

PNEUMONIA IN ADENOVIRAL INFECTIONS

Pneumonia has been frequently observed in association with infection by adenoviruses particularly types 4 and 7 among military recruits The clinical characteristics of the disease are similar to those of primary atypical pneumonia but significant increases in titer of cold hemagglutinins or of agglutinins for streptococcus MG do not occur

For further information see the section on Common Upper Respiratory Disease

PNEUMONIA CAUSED BY UNIDENTIFIED VIRAL AGENTS OR AGENTS PRESUMED TO BE VIRUSES

PNEUMONIA IN INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is generally considered to be a viral disease although the etiological agent has not been isolated and identified A more or less extensive bronchopneumonia may sometimes accompany the infection though it is rarely a dominant feature Respiratory symptoms

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Other Forms of Acute Bacterial Pneumonia

The pneumonias produced by staphylococci streptococci or Klebsiella (Friedlander s bacillus) are described in the sections devoted to infections with these bacteria

Pneumonia Due to Viral Agents

A primary type of bronchopneumonia may be caused by numerous known viruses as well as by at least one species of rickettsia and may also result from infections which are presumably viral in nature even though the specific agents have not yet been definitively isolated and identified These diverse etiological forms of nonbacterial pneumonia have become increasingly prominent and important within recent years largely as a consequence of progressive improvements in antibacterial chemotherapy together with wider diagnostic use of serological procedures and the newer methods of tissue culture The clinical features in most cases can be readily distinguished from those that characterize primary bacterial pneumonia and they apparently depend not so much upon which viral agent is responsible as they do upon the nature and the extent of pulmonary involvement including in some instances the occurrence of superimposed bacterial infection Thus the physician is confronted with a situation in which different viral agents may cause identical patterns of pulmonary disease or the same agent may give rise to a pneumonitis that varies considerably in its clinical aspects The difficulty of the problem is further increased by the fact that precise etiological diagnosis depends upon isolation of the causative agent or demonstration of a specific antibody response Both of these procedures require somewhat specialized laboratory techniques as well as an element of time particularly for serological tests which often makes their results useful only in retrospective analysis of the patient s illness Moreover it is obviously impossible exactly to determine etiology in those cases for which as yet unidentified viral agents are responsible

As Reimann has indicated the nomenclature of this group of pulmonary infections is of more than semantic interest Through habit convenience and the all too frequent lack of adequate diagnostic information the loose expression atypical pneumonia" has become popular as a general descriptive term But it must be emphasized that these etiological and clinical entities are typical in their own right and are atypical only when compared with classic pneumococcal pneumonia The writer agrees with Reimann that viral pneumonia is a more appropriate designation and that it is "broad enough to cover all viral pulmonary infections and tentatively those of probable viral origin in anticipation of the discovery of their causes An exception may currently be made for primary atypical pneumonia is discussed under Psittacosis ment of cold hemagglutinins

PNEUMONIA CAUSED BY KNOWN VIRUSES AND RICKETTSIAE

PSITTACOSIS

(Ornithosis)

Pneumonia may be caused by several closely related viruses of the psittacosis lymphogranuloma group This form of pneumonia is discussed under Psittacosis (p 43)

VIRUS INFLUENZAL PNEUMONIA

Since the identification of the virus of influenza by Smith Andrewes and Laidlaw in 1933 widespread epidemics localized outbreaks and sporadic cases of this disease have been repeatedly recognized in nearly all parts of the world Influenza is now known to be caused by a group of viruses most of which can be classified as either influenza A or influenza B according to their antigenic characteristics At least two other antigenic types of virus are known to exist The infection typically causes a grippelike syndrome with sudden onset

normal persons and of those suffering from acute infections of the respiratory tract without pulmonary involvement Moreover in the transmission experiments previously mentioned the microorganism was isolated from human volunteers with equal frequency both before and after successful inoculation It should also be noted that streptococcus MG is quite susceptible to penicillin whereas penicillin has no effect on the course of primary atypical pneumonia

Epidemiology The disease tends to occur in sporadic form but numerous localized outbreaks have been reported especially in semiclosed and crowded population groups such as schools and military establishments Among personnel of the armed forces it was more common than all other forms of pneumonia during World War II Epidemiological studies and transmission experiments indicate that the disease is spread directly from person to person via the respiratory route by infected discharges from the nose and mouth The communicability is often low and there is usually no history of contact In early epidemiological surveys the frequent failure to establish a history of contact was puzzling until it became apparent that there are many mild or unrecognized cases of the disease Patients hospitalized on open wards rarely transmit their infection to other patients but the relatively high incidence among physicians nurses and other hospital personnel serves to emphasize the importance of contact as well as the frequency of exposure in transmission Occasionally the disease seems to have an enhanced communicability in which case the history of antecedent contact may be readily obtained and the patients appear to transmit their disease more easily to other persons The factors responsible for this phenomenon have not been determined

All age groups are affected but the disease is recognized most frequently among persons in early or middle adult life There is no predilection for sex race or color The disease is widespread in the northern temperate zone and is relatively rare in the tropics Cases occur throughout the year although the greatest incidence is during the winter months In some years the disease has been prevalent during middle and late summer but in general it tends to parallel the combined incidence of upper respiratory tract infections The factors which influence susceptibility and resistance have not been established

The period of communicability is unknown One attack appears to confer at least temporary resistance to reinfection but the duration and quality of such immunity have not been determined The occasional occurrence of second attacks after an interval of apparent health indicates that immunity does not persist indefinitely in all patients

Morbid Anatomy Since the mortality rate is low there has been relatively little opportunity to study pathological changes in the lungs or elsewhere in the body The available postmortem studies indicate that the pulmonary lesions are not distinctive and probably cannot be differentiated from those of psittacosis Q fever and other nonbacterial pneumonias Characteristically there is a more or less extensive patchy bronchopneumonia with areas of hemorrhagic consolidation in various stages of evolution The bronchi appear inflamed and contain mucoid or mucopurulent exudate Localized atelectasis or emphysema may be present as the result of bronchial obstruction The pleura may show patches of fibrinous exudate and occasionally the pleural cavity contains small amounts of fluid Large pleural effusions are uncommon Enlargement of the tracheobronchial lymph nodes has been observed in some cases

Microscopic examination generally reveals an interstitial type of pneumonia most prominent in regions adjacent to bronchi and bronchioles The alveolar septums appear thickened with dilatation of the capillaries infiltration by lymphocytes and monocytes and varying degrees of edema Polymorphonuclear leukocytes are relatively few The alveolar spaces contain some edema fluid or a scanty exudate in which either mononuclear cells or erythrocytes may predominate Bacteria appear to be absent or are few in number Occasionally the alveoli and smaller bronchioles may be lined by hyaline membranes Peribronchial and perivascular infiltration by mononuclear cells is sometimes marked in extent The epithelium of the bronchi is usually intact although areas of necrosis and sloughing may be seen particularly in the smaller bronchi and bronchioles In these areas of necrosis polymorphonuclear cells are numerous Large numbers of polymorphonuclear cells are also seen in the exudate within bronchial lumina Intracellular inclusion bodies and elementary bodies have not been demonstrated

In some cases clinical evidence of encephalitis has been accompanied by demonstrable lesions of the brain Microscopic

are usually mild or absent and the pulmonary involvement may be discovered only incidentally on roentgenographic examination

PNEUMONIA IN ERYTHEMA EXUDATIVUM MULTIFORME

A nonbacterial pneumonia occurs frequently in the more severe forms of erythema exudativum multiforme (Stevens Johnson syndrome) although it rarely occurs in milder forms of the disease as originally described by Hebra The pneumonia is considered to be an integral part of the disease and in its clinical features closely resembles primary atypical pneumonia The etiology has not been determined but it is generally believed that the causative agent is a virus In some cases there is evidence that infection with the virus of herpes simplex may have been responsible

PRIMARY ATYPICAL PNEUMONIA

Definition Primary atypical pneumonia is an acute infectious disease of the human respiratory tract in which pulmonary infiltration of varying degree is a prominent feature The causative agent is in all probability a virus although it has not been definitely isolated and identified Certain other viral and rickettsial diseases of known etiology may clinically resemble primary atypical pneumonia including psittacosis or ornithosis influenza lymphocytic choriomeningitis and Q fever

History There is some indication that primary atypical pneumonia is not a disease of recent origin but possibly has existed for a century or more However in the older literature it is impossible to distinguish this form of pneumonia from influenza and many other infections of the respiratory tract Contemporary knowledge began to accumulate between 1930 and 1940 when a series of reports were published which described localized outbreaks of the disease emphasized its apparently rising incidence defined its clinical characteristics and presented evidence that none of the usual bacteria were etiological factors An important factor in the recognition of primary atypical pneumonia was the introduction between 1938 and 1940 of sulfonamide derivatives for the successful chemotherapy of pneumococcal and streptococcal pneumonia The failure of primary atypical pneumonia to respond to treatment with these drugs and later to the even more effective drug penicillin clearly established its distinction from the common bacterial pneumonias and contributed greatly to its present classification as a clinical and etiological entity

Etiology There seems little reason to doubt that primary atypical pneumonia is caused either by a single virus or by a group of closely related viruses During World War II carefully controlled experiments by the Commission on Acute Respiratory Diseases showed that the disease could be transmitted from man to man by spraying the nose and throat of healthy human volunteers with pooled sputum and throat washings collected from active cases Transmission was effected not only with these untreated inocula but also with the same materials freed of bacteria by passage through sintered glass or Seitz filters The characteristic illness which resulted in a considerable proportion of the subjects was again successfully passed from them to fresh volunteers by the same method Of great interest was the fact that minor respiratory illnesses differing from primary atypical pneumonia also developed in other subjects of the same experimental group This raised the question whether the same filterable agent could be responsible for several clinical varieties of infection or whether the inocula actually contained more than one type of virus The results of later studies by the Commission indicated that the latter possibility was probably correct although it is still uncertain whether all cases of primary atypical pneumonia are caused by a single infectious agent

Many attempts have been made in the laboratory to transfer the infection from man to a wide variety of mammalian and avian species None have been unequivocally successful Eaton and his associates claimed the isolation of a virus which produces pulmonary lesions in cotton rats and hamsters can be propagated in the developing chick embryo and is specifically neutralized by the convalescent serums of patients

No bacteria have been identified as etiological factors although pneumococci hemolytic streptococci staphylococci and more rarely other pathogens may be recovered in cultures of the throat or sputum early in the disease Thomas and his coworkers isolated a serologically distinct nonhemolytic streptococcus (streptococcus MG) from the lungs of fatal cases of primary atypical pneumonia and demonstrated specific antibodies to this microorganism in the blood of about 50 per cent of patients during their convalescence These observations led to the hypothesis that streptococcus MG might play an etiological role by functioning as a symbiont together with a virus in a manner analogous to the role of *Hemophilus influenzae* in swine influenza Later studies have shown however that streptococcus MG occurs not infrequently in the upper respiratory tract of

tients During or after the illness the serums of the majority of patients contain increased titers of cold hemagglutinins or of agglutinins for streptococcus MG

Clinical Course The clinical course of primary atypical pneumonia is variable ranging from a mild febrile illness of a few days duration to a severe disease with high temperature which may continue for several weeks In the average case of moderate severity the temperature is elevated for about ten days and falls to normal by lysis Symptoms usually abate as the fever declines although physical and roentgenographic signs of pulmonary involvement usually do not resolve completely until the temperature has been normal for several days A distressing paroxysmal cough is a characteristic feature of the disease and sometimes persists until the pulmonary lesion has cleared entirely The patient s convalescence may be prolonged by sensations of weariness and ease of fatigue

Complications are relatively uncommon Secondary bacterial infection occurs so infrequently that the disease seems almost to predispose against it Large pleural effusions are rare Otitis media sinusitis stomatitis tonsillitis bronchiectasis empyema pericarditis and myocarditis have been described Peripheral circulatory collapse has been noted Meningo-encephalitis has been observed clinically and at necropsy In a few cases especially those with high titers of cold agglutinins an acute hemolytic anemia has developed The anemia has appeared usually in patients treated with the sulfonamide drugs but has also been seen in patients who received symptomatic therapy alone its mechanism is not well understood but may be associated in some way with a high titer of cold agglutinins

Prognosis The prognosis in primary atypical pneumonia is excellent Although a few instances of death have been reported the uncomplicated disease is self limited in the vast majority of patients including those who may appear severely or even critically ill

Diagnosis No specific diagnostic procedures are available but in most cases the diagnosis can be established with reasonable certainty by adequate clinical roentgenographic and laboratory studies The disease may be strongly suspected from the following features gradual onset fever relative bradycardia normal respiratory rate paroxysmal cough and roentgenographic evidence of pneumonia with absent or few physical signs Failure to respond to treatment with penicillin adds support to the diagnosis but is not a completely reliable criterion Corroborative laboratory findings are a normal or only slightly elevated leukocyte count and normal bacterial flora on culture of the throat or sputum Tests for cold hemagglutinins are helpful in making a definite diagnosis since these peculiar antibodies appear exceptionally in diseases other than primary atypical pneumonia Cold hemagglutination may be demonstrated in approximately 55 per cent of patients although the incidence and magnitude of the titer varies according to the severity and duration of the illness For example the reaction becomes positive in over 90 per cent of patients in whom the disease is severe or prolonged but is positive in only about 20 per cent of mild cases The hemagglutinins do not appear in the serum until the second or third week after onset and the test is therefore of value only in making a late or retrospective diagnosis It is advisable to examine the patient s serum repeatedly for cold hemagglutinins at intervals of five to seven days since a significant rise in titer is more important than a single positive test Tests for agglutinins of streptococcus MG may also be made although these antibodies develop somewhat less frequently than do cold hemagglutinins If either or both of the tests become positive the patient almost certainly has suffered from primary atypical pneumonia but if both are negative it may be difficult or impossible to reach a definite diagnosis

Psittacosis Q fever influenza and adenoviral infections with pulmonary involvement may closely resemble primary atypical pneumonia Pneumococcal pneumonia and other acute bacterial infections of the lung not infrequently present similar clinical manifestations especially during the onset and early stages of their development In some cases pulmonary tuberculosis and mycotic infections of the lung must also be considered These diseases can nearly always be identified however either by isolation of the responsible agent or by the eventual demonstration of specific antibodies in the patient s blood Bronchogenic carcinoma pulmonary infarction and bronchiectasis occasionally must be included in the differential diagnosis

Treatment Several studies have indicated that the tetracycline drugs may exert a favorable therapeutic effect on the disease but there is some controversy in the literature concerning the validity of these observations In the writer s opinion if the diagnosis seems reasonably certain the

examination has shown focal hemorrhages perivascular cuffing with mononuclear cells and proliferation of astrocytes and glial cells There is some question whether these changes are directly caused by the viral agent or whether they represent a non specific tissue reaction which has been seen occasionally in other infectious diseases

No pathological alterations of note have been described in other organs or tissues

Symptoms The incubation period usually varies from two to three weeks In most cases the onset is gradual although occa sionally it may be abrupt During the early stages of the illness the symptoms are not distinctive and generally consist of fever cough headache malaise and chilly sensa tions Headache is often distressing or severe Shaking chills and sweats some times occur Sore throat is not uncommon *Cough is an outstanding feature and its absence makes the diagnosis questionable* The cough at first is dry and paroxysmal but later it usually becomes productive of mucoid or mucopurulent sputum The spu tum is not infrequently blood streaked and in rare instances may be frankly bloody or rusty in appearance Pain in the chest usually substernal in location and aggra vated by cough occurs in many cases However typical pleuritic pain is relatively uncommon Anorexia is often complained of and some patients have nausea and vomiting

Physical Findings Most patients appear to be acutely but not seriously ill although exceptions to this rule occur The tempera ture may range from 99 to over 105 F but is usually between 102° and 104° F at the height of the disease The fever curve may be either sustained or remittent in type

A relative bradycardia is observed in more than 50 per cent of patients and is of some diagnostic value The respirations are usually either normal or only moderately increased but in severe cases there may be dyspnea and cyanosis The nasal and pharyngeal mucous membranes often ap pear inflamed Examination of the chest almost always reveals fewer abnormal signs than would be expected from the roentgeno graphic findings Some dullness on per cussion may be found over the affected pulmonary area Harshness or diminution of the breath sounds may be detected Fine or medium rales are usually present and may be the only abnormal signs as the dis ease progresses they frequently become coarse and moist Rhonchi are sometimes heard and occasionally may be sharply localized and intensified on forced expira tion indicating bronchial obstruction Pleural rub and signs of pleural effusion are uncommon The spleen becomes pal pable in rare instances

Roentgenographic Findings The pulmo nary lesions as seen on roentgenograms vary widely in character and distribution The abnormal shadows may appear mottled feathery or uniformly opaque with differ ing degrees of density In the majority of cases the lesions are most dense in the hilar region and become less dense toward the periphery of the lung field The margins of the pneumonic areas are usually poorly defined The lower lobes are most fre quently involved although any part of the lungs may be affected In about 50 per cent of patients the disease is confined to one lobe but in the remainder more than one lobe is affected Occasionally the pneu monia is migratory and spreads from lobe to lobe with clearing in one area as exten sion occurs in another There is nothing characteristic about the roentgenographic changes and a similar picture may be pro duced by many other infections of the lung including pulmonary tuberculosis

Laboratory Findings In the majority of cases the total leukocyte count is within normal limits although a slight leukopenia or a moderate leukocytosis may be found The differential count may show a mod erate increase in polymorphonuclear leuko cytes but rarely to the degree seen in bacterial pneumonias Occasionally a brisk leukocytosis is seen during convalescence in the absence of a detectable secondary bacterial infection The erythrocyte count and hemoglobin values are seldom reduced except in severe prolonged cases or in rare instances of acute hemolytic anemia The urine may contain a little protein and a few cellular elements as in other infec tious diseases The erythrocyte sedimenta tion rate usually is moderately elevated at the height of the disease but falls slowly to normal during convalescence Bacterio logical examination of the sputum ordi narily reveals only those microorganisms found normally in the upper respiratory tract Pneumococci of the higher types may be present In many cases the bacterial con tent of the sputum is remarkably scanty Unlike pneumococcal pneumonia the serum chloride levels as well as the chlo ride excretion remain within the normal range Transitory weakly positive Wasser mann and other serological tests for syph ilis may be obtained with the acute or convalescent phase serums of some pa

the only product of group A streptococci which is of recognizable significance in the pathogenesis of any of the clinical manifestations of streptococcal disease This substance is responsible for the erythema in scarlet fever Persons susceptible to its action may be detected by the injection into the skin of a small amount of a suitable dilution of culture filtrate of a group A streptococcus A small area of redness will develop within twelve hours in positive reactors This is the *Dick test*

Strains of group A streptococci may be segregated into numbered types by serological methods devised by Griffith and Lancefield Antibacterial immunity is type specific probably long lasting and protects against subsequent reinfection by a strain of the same type None of the antibodies which develop in response to stimulation by the extracellular substances described above seems to influence the parasitism of human beings by group A streptococci

History Sydenham is often stated to have described scarlet fever but the early accounts are inadequate and inexact Certainly this disease the intimately related tonsillitis and pharyngitis without a skin rash and erysipelas had been recognized for many years before the discovery of *Streptococcus pyogenes* by Rosenbach in 1884 Significant understanding of streptococcal infections began with the discovery by Schottmuller in 1903 that certain strains produced hemolysis on blood agar Brown in 1919 defined this reaction in greater detail and coined the descriptive terms that are still in use

The streptococcal etiology of scarlet fever and tonsillitis was quite well established by 1895 Certain Russian investigators had immunized large numbers of children with various streptococcal products and treated many cases of scarlet fever with antiserum in the first years of this century All of this information was discarded throughout most of the world for many years It was held that the hemolytic streptococci present in the throats of patients with scarlet fever were secondary invaders and that tonsillitis could be caused by a large number of different bacteria

The re-establishment of the streptococcal etiology of scarlet fever by the Dicks and Dochez led to renewed interest in the whole subject and Bloomfield clearly defined the streptococcal etiology of nearly all cases of tonsillitis The unravelling of the whole spectrum of streptococcal respiratory infection and the important nonsuppurative complications has been accomplished since 1935 This was stimulated especially by the serological classification of the organism by Lancefield and Griffith and by the great epidemics of streptococcal disease in the armed forces in World War II which supplied an enormous volume of clinical material The careful studies of these disorders in children by Powers and his associates have also been most provocative with respect to the mechanism of the different patterns of streptococcal disease at different ages

Epidemiology Group A hemolytic streptococci are the only significant cause of nonpneumonic bacterial respiratory infections in children over the age of five and in adults There is a surprising lack of information in regard to the etiology of this type of infection in infants and young children

Nearly all respiratory infections in all age groups are caused by filterable viruses The proportion of streptococcal infections varies with the season of the year and the geographical location In the United States the peak incidence is between December and May The North Atlantic states a broad area around the Great Lakes and belts running north and south along both sides of the Rocky Mountains appear to be the areas most propitious to the spread of group A streptococci

Approximately 10 per cent of nonpneumonic respiratory infections that are sufficiently severe to bring the patient to the attention of a physician are due to hemolytic streptococci If *all* such respiratory illnesses in a middle class population are considered it is found that only about 2 per cent are the result of infection by these organisms

In any season in any community the same serological types of group A hemolytic streptococci are responsible for all varieties of disease caused by these organisms There is no specific streptococcus of scarlet fever sore throat erysipelas cellulitis or puerperal sepsis although certain strains at certain times seem quite incapable of producing a rash It is not known whether this is a fixed characteristic of these organisms

Quantitatively upper respiratory infections including scarlet fever pharyngitis and tonsillitis are the only important forms of group A streptococcal infection Illness in these categories occurs most frequently in children from five to fifteen years of age but younger and older persons are highly susceptible to infection

Transmission of group A streptococcal infections usually occurs as the result of direct contact between infected persons or healthy carriers and susceptible persons Significant extra human or animal reservoirs of these organisms do not exist although many outbreaks due to contamination of an article of food often milk have occurred The incubation period is two to three days

Children among whom infection is commonplace and healthy carriers are abundant are primarily responsible for the spread of streptococcal disease The introduction of an untreated infected five year old into a family will be followed by infec

patient should receive either tetracycline chlortetracycline or oxytetracycline in doses of 0 5 gm every six hours until the temperature falls to normal The dosage may then be reduced to 0 5 gm twice daily but treatment should be continued for at least another three days If side reactions such as nausea vomiting and diarrhea occur it may be necessary to reduce the amount of drug or to discontinue therapy entirely

Symptomatic therapy may include codeine in doses of 0 03 to 0 06 gm to control cough Inhalations of steam are helpful in relieving soreness and dryness of the upper respiratory passages Salicylate compounds should be used cautiously since some patients respond badly to their use When the disease is severe with respiratory embarrassment oxygen therapy is usually indicated During convalescence it is recommended that the patient be kept at bed rest for several days after the temperature is normal since early ambulation may be followed by symptoms of weakness lassitude and easily induced fatigue

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Streptococcal Infections

Introduction

Streptococci commonly cause disease particularly of the respiratory tract in man The most simple classification of these organisms and the one most useful for clinical purposes is based on their action on blood agar plates *Beta* hemolytic streptococci are those able to produce a completely clear zone around the colony The term *alpha* hemolysis indicates that there is hemolysis circled by a green ring surrounding the central colony This appearance characterizes the organisms known as *Streptococcus viridans* Many streptococci are completely nonhemolytic

The *alpha* hemolytic and nonhemolytic streptococci are normal inhabitants of the upper respiratory tract of man from a few hours after birth until death and may also be recovered from the feces Many require reduced oxygen tension for initial isolation Infection by these streptococci is unusual except in bacterial endocarditis and in suppurative disease arising by direct extension of the organisms from the upper respiratory tract colon or female genital organs In these circumstances such disorders as paranasal sinusitis and cerebral or intra abdominal abscesses may develop

The most important of the streptococci are those that produce *beta* hemolysis on blood agar Organisms having this characteristic may be segregated into lettered groups by the use of a precipitin reaction described by Lancefield Those of the greatest significance in human disease are the members of group A These organisms often parasitize and cause disease of the respiratory tract of previously healthy persons

Hemolytic streptococci of the other groups are less important Nonhemolytic or *alpha* hemolytic varieties of many have been described following the original studies of Lancefield that were carried out with hemolytic strains Organisms of groups B and D may cause bacterial endocarditis and infection of the urinary tract Members of group D are the enterococci the common streptococci present in the normal colon Streptococci of the other lettered groups C E F G H K L M and N are most often discovered in the flora of the upper respiratory tract and rarely cause human disease

Group A streptococci form an extraordinary variety of extracellular substances many of which stimulate an immune response in the infected individual Measurement of certain of these antibodies such as antistreptolysin O antistreptokinase and antihyaluronidase are of importance in the study of streptococcal disease and its complications The erythrogenic toxin is

complication which develops after the first week is likely to be the result of a reinfection and a different type will be recovered from the purulent exudate

Bacteremia was once observed rather frequently during the course of streptococcal respiratory infection and was often associated with metastatic lesions in the joints bones and elsewhere Such cases are now almost unknown even if antimicrobial therapy is withheld Similarly there has been a nearly complete disappearance of group A streptococcal meningitis Pneumonia has always been a surprisingly uncommon complication of streptococcal upper respiratory infections

Tender cervical adenitis is regularly present and is not to be regarded as a complication unless the lymph nodes become very large and suppuration is imminent

All of the various suppurative streptococcal complications may be prevented by early and adequate antimicrobial therapy Response to similar management is excellent if any should develop in an untreated patient

Nonsuppurative Complications Antimicrobial therapy has made the management of acute hemolytic streptococcal infection of all types a simple matter Suppurative complications are readily prevented by appropriate treatment and are in fact rarely seen in the United States today For this reason the greatest interest in disease caused by these organisms has centered recently about the poststreptococcal sequelae that are included in the group of nonsuppurative complications

Most important of these are *rheumatic fever glomerulonephritis* and *mesenteric adenitis* All occur one to three weeks after the complete subsidence of the initial streptococcal illness In none is there evidence of dissemination of the organism from the throat or other area of primary infection to the affected internal organs nor does the pathological anatomy of these processes suggest a suppurative disorder

There can be little doubt any longer that all of these disorders are complications of group A hemolytic streptococcus infection but their pathogenesis is poorly understood It is now evident that strains of only a few types of group A hemolytic streptococci are able to cause glomerulonephritis but nearly all strains are rheumatogenic Many investigators believe that an inappropriate immunological reaction is responsible for these diseases and that this may well require repeated exposure of the individual over some period of time to different types of group A streptococci It is noteworthy that rheumatic fever and nephritis are rare complications of streptococcal infection before the age of four to five years

Approximately 3 per cent of streptococcal infections which have occurred in well studied epidemics have been followed by the development of rheumatic fever The incidence of glomerulonephritis in outbreaks caused by nephritogenic strains of streptococcus has been much greater

All of the recognizable clinical manifestations of rheumatic fever may be prevented by adequate treatment of the initial streptococcal illness with an appropriate antimicrobial agent It is not yet known whether this can also be accomplished for glomerulonephritis but preliminary study suggests that the incidence of this disease will also be reduced

Treatment The management of the various streptococcal illnesses should include those general measures that are applied in all acute infections Bed rest light or liquid diet if angina is present and severe and adequate but not excessive fluid intake are indicated Gargles are of little value but considerable relief of sore throat may be obtained by the use of hot saline throat irrigations Acetylsalicylic acid in a dose of 0 3 to 0 9 gm every three to four hours is often of great symptomatic benefit

Most important is the prompt institution of appropriate antimicrobial therapy which has four goals (1) the prompt control of the acute suppurative process in the respiratory tract or elsewhere (2) the prevention of suppurative complications (3) the prevention of nonsuppurative complications and (4) the elimination of the carrier state and the prevention of transmission of the organism to others The third and fourth will be fully attained only if the organism is permanently eradicated from the tissues This can best be accomplished by the administration of penicillin and less well by the use of erythromycin and tetracyclines Sulfonamides are not effective and novobiocin is too toxic for use in treatment of streptococcal infection No examples of penicillin erythromycin or tetracycline resistant group A streptococci have been described It is essential that full doses be given over a period of ten days regardless of the drug used

Penicillin is preferred and should be used in every case unless the patient is known or believed to be sensitized to it It should be administered in one of three ways if an uncomplicated respiratory infection is under treatment

tion of more than half of his siblings and a significant number of adults in the household Hamburger and his associates have shown that a patient or healthy carrier who harbors hemolytic streptococci in the nose is most likely to contaminate the environment with these organisms and to transmit disease

The problem of control of hemolytic streptococcal disease is complicated by the fact that a very large proportion of infections by these organisms are either exceedingly mild or completely inapparent Persons with this type of illness are fully capable of disseminating the streptococci but will not come under the care of a physician who could apply modern chemotherapy eradicate streptococci from the pharyngeal tissues and eliminate the possibility of transmission of disease

The Nature of Streptococcal Respiratory Infection When group A streptococci parasitize the upper respiratory tract of human *beings they multiply most freely in the* lymphoid tissue of the pharynx and the tonsils The subsequent illness is presumably the result of the release of substances at this site which are injurious to the local tissues and which produce systemic disturbances The nature of the response to infec*tion is conditioned by the age of the* subject and his previous exposure to streptococci

Group A streptococcal respiratory infections in infants and small children lack an acute and well defined onset have rhinorrhea as a dominant manifestation are rarely associated with high fever and run a protracted and indeterminate course The *physical signs in the throat are nondescript* and usually do not permit an accurate clinical diagnosis Suppurative complications such as otitis media and cervical lymphadenitis occur frequently A rash is rarely observed

The disease in older children is quite different The onset is often acute with high fever sore throat is the predominant symptom and typical exudative tonsillitis and pharyngitis are usually present A rash (scarlet fever) is often discovered Suppurative complications decline in frequency *with advancing* age Adults experience an illness much like that of older children except that a rash or suppurative complications of any kind rarely occur

Powers and his associates proposed and subsequent investigations have supported but not established the hypothesis that these changing patterns of streptococcal illness which occur with advancing age are the result of repeated infection by different types of group A streptococci rather than simple maturation of the host It has been suggested that an immunological mechanism involving the development of hypersensitivity to certain of the products of the streptococcus may be responsible

Diagnosis of Streptococcal Infection The precise diagnosis of hemolytic streptococcal infection requires measures beyond clinical examination and simple laboratory procedures Of greatest importance and presenting the greatest difficulties is the recognition of streptococcal upper respiratory infection especially in young children Bacteriological study of material obtained from the nasopharynx is very often essential

Swabs should be passed through the mouth under direct vision using a good light and rubbed over the tonsils and posterior pharynx *before any antimicrobial therapy is administered* The swab should *be streaked directly with a minimum of* delay on sheep blood agar plates of low dextrose content After incubation the number of hemolytic streptococci present should be recorded in a roughly quantitative manner These organisms will be very numerous in nearly all cases if they are the cause of the *infection The presence* of a few does not provide convincing evidence that they are responsible for the illness because 5 to 10 per cent of the general population are nasopharyngeal carriers of these organisms Their absence may be regarded as excluding streptococcal disease Serological grouping and typing of the isolated organisms is not necessary for routine clinical study

Additional information may be obtained in selected cases when indicated by serial measurement of antibody titer (antistreptolysin O) over a period of four to six weeks A significant increase provides positive evidence *of the presence of a hemo*lytic streptococcal infection

Suppurative Complications Direct extension of the hemolytic streptococcus from the locus in the throat to the surrounding tissues may result in certain suppurative complications Paranasal sinusitis otitis media mastoiditis suppurative cervical adenitis and impetigo are the most common and will occur most frequently in untreated children less than four years old

It has been demonstrated that otitis media occurring early in the course of streptococcal respiratory infection is caused by the same serological type that was pres*ent in the throat at the onset* A similar

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Hemolytic Streptococcal Sore Throat

The general term "hemolytic streptococcal sore throat is often used to describe the various forms of nonpneumonic group A streptococcal respiratory infection Among these scarlet fever and tonsillitis are distinguishable entities It should be emphasized that there is a spectrum of disorders in this broad category which depend upon the age of the patient his previous experience with group A streptococci and the presence or absence of tonsils and which often may not be differentiated readily from one another

A rash is present in only a small percentage of clinically recognizable streptococcal infections The frequency will vary with the age of the affected population and the scarlatinogenic potentialities of the infectious agent If the enormous numbers of mild atypical and inapparent streptococcal illnesses which are rarely associated with erythema are considered it becomes apparent that scarlet fever is an unusual manifestation of streptococcal respiratory infection in the United States

Patients who develop a rash are on the average more sick than those who have tonsillitis or pharyngitis without a rash but there is substantial overlapping in the degree of severity of illness in the two groups There will be no difference in the incidence of suppurative or nonsuppurative complications in persons of comparable age

Erythema is unusual before the age of three and in adolescents and adults It cannot be emphasized too strongly that antitoxic immunity against the erythrogenic toxin confers no protection against subsequent infection by other types of group A streptococci

Acute Tonsillitis and Pharyngitis

Acute tonsillitis and pharyngitis are inflammatory processes of the lymphoid tissue of the pharynx usually caused by group A hemolytic streptococci A form of nonbacterial tonsillitis and pharyngitis occurs probably caused by an adenovirus which may be most difficult to distinguish from streptococcal disease It often occurs in epidemics (see page 9)

Morbid Anatomy and Pathology There is a ring of lymphoid tissue encircling the pharynx which includes the palatine and lingual tonsils and the adenoids Similar tissues are situated widely over the pharyngeal walls in smaller masses It is believed that all of these areas are involved in most cases of streptococcal pharyngitis In many instances the faucial tonsils become particularly swollen and covered with a purulent exudate and exudative tonsillitis is the result

The essential lesion is a suppurative one with inflammation and swelling of the affected areas and with outpouring of leukocytes and fibrin Very often they combine to form an extensive exudate

Etiology The bacterial form of exudative tonsillitis is usually caused by group A hemolytic streptococci Rare infections by strains of groups C and G have been described but there is no evidence that pneu

1 Benzathine penicillin G as a single intramuscular injection of 900 000 to 1 200 000 units
2 Oral penicillin four doses daily for ten days of 200 000 (125 mg) to 400 000 (250 mg) units of penicillin V or G The latter should be contained in a buffered tablet
3 Procaine penicillin with aluminum monostearate as a single intramuscular injection of 600 000 units every other day for three doses

Patients with more serious streptococcal infections such as severe tonsillitis scarlet fever those of the skin or lung or a suppurative complication of an ordinary respiratory infection should receive 600 000 to 900 000 units of procaine penicillin per day for several days until the illness is obviously subsiding when a shift to a single dose of benzathine penicillin or to oral penicillin may be made

The response of extrapharyngeal suppurative complications of streptococcal infection to penicillin is good and recovery without surgical intervention is the rule with one exception Sterilization of the local abscess in well established suppurative cervical adenitis is most difficult Incision and drainage is usually required in such cases unless spontaneous rupture occurs

When penicillin is contraindicated because of hypersensitivity it is proper to employ erythromycin by mouth in a dose of 250 mg four times a day for at least ten days Similar amounts of one of the tetracycline drugs may also be used but this is a less satisfactory regimen Severely ill patients may well receive 500 mg of erythromycin twice daily intravenously for a short time until it is certain that the drug will be accepted and absorbed when given by mouth Sulfonamides should not be used in the treatment of hemolytic streptococcal infections

Prophylaxis There are no simple preventive measures which may be applied to the control of streptococcal infections in the population at large Isolation and other standard public health procedures must always fail because of the huge numbers of carriers and missed cases particularly among children Many communities in the United States have abandoned quarantine of scarlet fever and other streptococcal diseases as fruitless

It is important to remember that hemolytic streptococci will have disappeared from the throat within a few hours after the administration of penicillin or another effective antimicrobial agent If treatment is prolonged adequately the carrier state will be eradicated in nearly all infected persons and carriers Tools are thus readily at hand for the prevention of transmission of streptococcal disease by recognizably infected persons or carriers

It is often desirable to prevent group A streptococcal infections in selected persons who are well These are persons who have had rheumatic fever or rheumatic heart disease and closed groups in schools and similar establishments and in the armed forces who are experiencing an outbreak of streptococcal disease

Unfortunately no form of immunization is of avail Tonsillectomy has been employed prophylactically in the past but is now known to be useless for this purpose since it does not prevent infection by hemolytic streptococci Subsequently acquired streptococcal respiratory illnesses may be less severe but the frequency of occurrence of nonsuppurative complications is not reduced

Chemoprophylaxis has proved to be highly effective and may be attained by one of three regimens listed below in order of their apparent efficacy and practicability

1 Benzathine penicillin G in a single injection of 1 200 000 units will provide protection for about thirty days
2 Sulfonamide in daily administration by mouth of 1 0 gm of sulfadiazine or one of the other sulfapyrimidines provides satisfactory prophylaxis but failures will occur Toxic reactions may be observed during the first sixty days of continuous treatment
3 Oral penicillin in daily administration of 200 000 (125 mg) units of penicillin G has been employed widely for prevention of streptococcal infection but failures have been as frequent as with sulfonamide therapy The same amount given twice daily is believed to be highly effective but the multiple doses create an overly complicated regimen There is insufficient experience with the better absorbed penicillin V to permit recommendations as to its proper use in streptococcal prophylaxis

Little is known of the possible role of the other potentially effective antimicrobial agents for this purpose and they should not be so used

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pharynx for long periods after recovery if antimicrobial therapy has not been employed The more detailed and elaborate the cultural procedures the more frequently they may be discovered and over longer periods of time The usual simple techniques will recover them in about 70 per cent of adults during the fourth week Their presence may be regarded as a public health hazard but does not prejudice the health of a patient who has recovered from a streptococcal illness

Complications Suppurative and nonsuppurative complications may follow untreated streptococcal tonsillitis and pharyngitis The former are unusual except in small children and the latter are rare in patients less than five years of age (see Introduction) Both may be prevented by appropriate antimicrobial therapy

Treatment Adequate and appropriate antimicrobial therapy should be administered whenever the diagnosis of group A hemolytic streptococcal tonsillitis or pharyngitis is reasonably certain on clinical and laboratory grounds (see Introduction) Every effort must be made to avoid the indiscriminate treatment of the more common viral respiratory illnesses many of which may be difficult to distinguish from streptococcal disease

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Scarlet Fever

Definition Scarlet fever is a form of group A hemolytic streptococcal infection of the upper respiratory tract The disease is similar to acute tonsillitis and pharyngitis caused by these organisms with the addition of an exanthem and an enanthem The etiology and epidemiology of the disease are discussed in the Introduction

Pathogenesis The pathogenesis of the skin rash in scarlet fever has been extensively investigated but no final conclusions have been reached One group of investigators has believed that the erythrogenic material has a direct toxic action on the skin which is neutralized by antitoxin Others have noted that infants are Dick negative even though no antitoxin is demonstrable in their serum and their mothers are Dick positive These and other observations have suggested that reactivity to the rash toxin may be of an allergic type acquired by previous contact with the hemolytic streptococcus Little is known of the pathogenesis of the other manifestations of scarlet fever The changing nature of streptococcal disease from infancy to adulthood which has been described in the Introduction strongly suggests that an alteration of general and local tissue reactivity occurs as the result of successive apparent or inapparent infections by hemolytic streptococci

Morbid Anatomy The essential lesion in scarlet fever is the suppurative process in the nasopharynx which is common to all forms of hemolytic streptococcal upper respiratory infection The dermal lesion is a hyperemia which is the result of toxic injury of the vascular endothelium leading to atony and dilatation There are also edema of the skin and aggregations of lymphocytes and monocytes particularly around the hair follicles Inflammatory exudate accumulates within the middle layers of the epidermis and accelerated keratinization occurs in this area This alteration in the skin leads to desquamation as the outer layer separates from the keratinized intermediate zone

Symptoms and Signs Scarlet fever except for the presence of a skin rash closely resembles the other forms of hemolytic steptococcal upper respiratory disease in comparable age groups The onset is usually abrupt often with a chill or chilly sensations Headache nausea and vomiting occur frequently Sore throat is the principal localizing symptom and is rarely absent It may be so severe that swallowing of even liquids is agonizing

In typical cases the mucous membrane of the throat is fiery red the intensity of the color usually seen in streptococcal sore throat being enhanced by the enanthem Otherwise the signs present in this area are identical with those previously described in the section on tonsillitis and pharyngitis The distinctive signs are limited to the pharynx the cervical lymph nodes and the skin The tongue may be bright and the papillae large (*raspberry tongue*) or coated with the red papillae protruding (*strawberry tongue*) These manifestations of the disease are rarely seen in adults Tender anterior cervical adenitis is regularly present even if the disease is mild Atypical cases are common

mococci micrococci or other organisms will cause this syndrome in older children or adults There is an amazing paucity of information about the etiology of this type of respiratory infection in infants and young children

Hemolytic streptococci are the only significant bacterial cause of nonexudative pharyngitis Many viral infections may mimic this clinical state making the study of upper respiratory infection without bacteriological control most difficult

Symptoms The onset of streptococcal tonsillitis and pharyngitis in older children and adults is usually quite abrupt but varies greatly in intensity Usually the first symptom is sore throat which may remain mild or rapidly become severe with great pain on swallowing The soreness may be unilateral or bilateral and is characteristically at the sides of the neck under the angles of the jaw Many patients with viral respiratory infections also have sore throat but careful questioning often reveals that the symptom is localized to the anterior neck over the trachea and larynx

Streptococcal respiratory infection is not accompanied by significant cough or by coryza The presence of either of these manifestations should suggest a different etiological diagnosis Rhinorrhea does occur especially in young children who frequently develop suppurative sinusitis

Very often there are chilly sensations or a chill near the onset with the appearance of fever which may be trivial or rise to 105° F Head back and muscle aching will be present in such circumstances

Signs Proper diagnosis of respiratory infection requires careful examination of the pharynx using a good light The typical signs *in a person whose tonsils are intact* are most characteristic The anterior pharyngeal tissues are swollen engorged and fiery red Often the uvula will resemble a red iridescent sac two to three times its normal size The tonsils are greatly enlarged may nearly meet in the midline and are covered with a thick creamy exudate which may be readily scraped off with a tongue depressor or swab That part of the posterior pharynx which is visible will also be red swollen and covered with exudate The anterior cervical lymph nodes at the angles of the jaw are swollen and tender in nearly all cases The clinical picture may be very similar if *the tonsils have been removed* except for the absence of the signs attributable to these organs

Many examples of streptococcal tonsillitis and pharyngitis do not present the complete picture just described Exudate may be present in very small amount or absent in less severe cases even though the tonsils are intact and edema may be slight Often in such cases the most useful signs will be the presence of redness of the throat and tender lymph nodes at the angles of the jaw

Laboratory Findings Total leukocyte counts greater than 12 000 per cu mm are the rule in typical hemolytic streptococcal tonsillitis and pharyngitis Unfortunately *there may be no abnormality in the* less severely ill patients who present the greatest difficulties in clinical diagnosis The erythrocyte sedimentation rate is usually quite rapid and the C reactive protein test is strongly positive Cultural study of the pharyngeal flora (see Introduction) is an invaluable guide to precise diagnosis

Differential Diagnosis Streptococcal tonsillitis in its typical form need be differentiated only from diphtheria nonbacterial exudative tonsillitis and infectious mononucleosis

Nonexudative tonsillitis and pharyngitis caused by hemolytic streptococci may resemble particularly in children certain of the nonbacterial respiratory illnesses Accurate clinical diagnosis even with great experience is most difficult The presence of marked sore throat leukocytosis and tender anterior cervical adenopathy should weigh the diagnosis toward streptococcal disease Cough coryza and rhinorrhea (in adults) make a nonbacterial disorder more likely Cultural examination of the throat is often necessary

Course The course of untreated hemolytic streptococcal tonsillitis and pharyngitis in older children and adults is benign *Seventy per cent of patients are afebrile* within seventy two hours after onset but sore throat abnormal signs in the pharynx and tender adenitis persist for two or three days after the return of the temperature to normal The latter event often occurs by crisis

The whole process is shortened by appropriate antimicrobial therapy by twenty four to forty eight hours the most dramatic effect being on the course of the fever and the least on the abnormal physical signs

Leukocytosis persists in more than one half of untreated patients for a week or more but disappears more quickly after the *institution of antimicrobial therapy* The erythrocyte sedimentation rate returns to normal in 80 per cent of patients by the third week

Hemolytic streptococci persist in the

fever may resemble that of diphtheria No rash is seen in the latter disease but it must be remembered that the two may occur simultaneously The erythema of *rubella* (German measles) and *rubeola* (measles) must be distinguished from that of scarlet fever *Infectious mononucleosis* with angina and a rash may easily be mis taken for scarlet fever if appropriate cul tural and hematological studies are not carried out The erythematous rashes of drug sensitivity are often similar to the dermal lesion of streptococcal disease The absence of other characteristic symptoms and signs of scarlet fever should permit their recognition in other than the most unusual case

Prognosis Scarlet fever in the United States at the present time is a relatively mild disease and the prognosis without antimicrobial therapy is uniformly good Suppurative complications are common in younger children but are well controlled by proper treatment Serious late nonsup purative complications must be anticipated during convalescence regardless of the severity of the initial illness if appropriate antimicrobial therapy has not been admin istered Rheumatic fever is most likely to supervene in patients with a past history of this disease

Treatment The treatment of scarlet fever is the same as that recommended for other streptococcal infections (see Introduction) If the disease is severe 600 000 to 900 000 units of procaine penicillin should be ad ministered daily for the first two or three days

In the past specific antitoxin was em ployed This involved the injection of an antiserum prepared by the immunization of horses with filtrates of group A hemolytic streptococci or of convalescent human serum The advent of potent antimicrobial drugs has made serotherapy largely un necessary The hazards accompanying the administration of foreign protein and the discomfort of the associated serum sickness suggest that horse serum antitoxin should rarely be used in the treatment of scarlet fever If indicated 15 000 to 30 000 units are to be administered intravenously or intramuscularly with the usual precautions Convalescent human serum should not be used because of the danger of serum hepa titis

The toxic and systemic aspects of scarlet fever are not quickly ameliorated by the administration of penicillin Improvement does begin shortly after this agent is ad ministered is well established within forty eight hours and may confidently be ex pected to continue to eventual recovery by the fourth day It is reasonable to conclude that serum therapy should be reserved for those rare cases in which extreme toxicity suggests that a fatal outcome might ensue before the effect of parenteral penicillin could manifest itself or for those patients in whom this agent has been given for forty-eight hours without evidence of benefit

Prophylaxis The prophylaxis of scarlet fever is that of other group A hemolytic streptococcal infections and is discussed in the Introduction Active immunity to the erythrogenic toxin may be attained in Dick positive persons by repeated injec tions of increasing amounts of the active material This procedure is not recom mended since protection is conferred only against the development of a rash and not against infection by hemolytic streptococci Furthermore reactions during immuniza tion are common and often severe

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Erysipelas

Definition Erysipelas is an acute group A hemolytic streptococcal infection of the skin which usually involves the face and head but may affect any area of the body

History Erysipelas has been known since very ancient times There was a great outbreak of the facial form of the disease in the Union Army during the Civil War during which more than 25 000 cases were reported to the Surgeon General

The communicability of the infection was rec ognized before the isolation of the etiological agent from the skin of sick persons by Fehleisen in 1882 He transmitted the illness to other human beings by the experimental inoculation of pure cultures of streptococci

Etiology and Pathogenesis Group A hemo lytic streptococci are the only significant organisms responsible for erysipelas al

particularly in persons in whom the tonsils have been removed Tonsillar and pharyngeal exudate edema and redness may be minimal or absent

The rash usually appears on the second day It consists of a diffuse bright scarlet erythema with many points of deeper red The *distribution is variable but the trunk* and inner aspects of the arms and thighs are most often affected In many cases the rash is well marked only in the axillae and groins The face is flushed and red but a pale area the *circumoral pallor* is often seen around the mouth The palms and soles are not erythematous Petechiae and occasionally ecchymoses are observed especially in severely ill patients The application *of a tourniquet to the arm for five minutes will be associated with the* appearance of large numbers of petechiae distal to the obstruction in nearly all cases This is *Rumpel Leede s sign* it is not specific for scarlet fever

Course The rash reaches its height as do the other manifestations of the disease on the third or fourth day after which there is the beginning of defervescence The erythema disappears by the sixth to ninth day in association with a return of the temperature and the throat to normal

Desquamation begins as a fine scaling of the face and body which is usually completed during the second week About this *time the extensive and characteristic des* quamation of the palms and soles starts and continues for one to two weeks

The course and clinical features of scarlet fever vary greatly with the severity of the disease Many mild cases are observed in which constitutional symptoms and sore throat are minimal fever is low grade and of short duration and the rash is evanescent A florid eruption is sometimes seen in persons in whom all other evidences of the disease are slight indicating that the reaction to the erythrogenic toxin *per se* is not primarily responsible for the systemic manifestations of scarlet fever

As the disease becomes more severe there is a general increase in the intensity of all symptoms and signs The maximum temperature in individual cases of the more severe forms will be 101 to 106 F The angina will be distressing and marked prostration evident The rash will usually be prominent but severe cases with little erythema are often seen

Malignant Scarlet Fever A toxic or malignant type of scarlet fever was regularly described in earlier studies of this disease A fulminating *course* was associated with delirium collapse and death—often within forty-eight hours The short duration of the disease did not permit the development of a typical *erythema but hemorrhages* in the skin were observed Such cases in which death occurred quickly without dissemination of the streptococci from the local focus in the throat are now rare Similarly septic scarlet fever or streptococcal sore throat with bacteremia metastatic suppuration in the joints and elsewhere and a prolonged and often fatal course has disappeared in properly treated cases

Complications The complications of scarlet fever are those common to all forms of hemolytic streptococcal upper respira*tory infection with or without a rash and are of two types the suppurative and the* nonsuppurative Both have been described in the Introduction

Relapse Relapse is unusual in untreated scarlet fever but reinfection with a new serological type of hemolytic streptococcus may occur at any time during convalescence and lead to an apparent exacerbation of tonsillitis and pharyngitis Recovery from scarlet fever is usually associated with a permanent immunity to the rash toxin and second attacks are rare It must be emphasized again that protection against subsequent infections by other types of hemolytic streptococci is not conferred *and episodes of tonsillitis and pharyngitis* occur frequently in persons who have had scarlet fever

Diagnosis The recognition of scarlet fever in its characteristic form is *not dif* ficult The presence of angina tonsillitis anterior cervical adenitis and erythema permits a clinical diagnosis in many instances Cultural examination of material obtained from the nasopharynx is essential in atypical cases (see Introduction)

The injection of 0 1 ml of scarlet fever antitoxin or of 0 2 to 0 3 ml of convalescent human serum into an area where the rash is florid will be followed by blanching around the site of injection in eight to twelve hours This is the *Schultz Charlton reaction* It is inadvisable to perform this test with human serum because there is substantial danger of transmission of serum hepatitis Streptococcal antitoxin is no longer readily available Usually clinical and bacteriological study suffice for diag*nosis*

Polymorphonuclear leukocytosis is the rule in moderately severe and severe scarlet fever but is often absent in mild cases

The local pharyngeal lesion in scarlet

Complications The most important complication of untreated facial erysipelas is local abscess formation in some part of the involved skin which develops in 5 to 10 per cent of these patients Rheumatic fever is an extraordinarily infrequent complication of erysipelas but glomerulonephritis is less so Untreated patients may relapse a few days after apparent recovery It is probable that all of these complications can be prevented by adequate treatment but detailed studies of large numbers of cases of erysipelas managed by the use of modern antimicrobial agents are not available

Persons who have suffered an attack of erysipelas are quite likely to undergo similar illnesses at irregular intervals throughout their lives

Prognosis Untreated erysipelas was highly lethal for children less than two and persons over sixty years of age and in those with serious underlying debilitating disease Generalized sepsis with bacteremia and widespread dissemination of the infection was the usual sequence of events Prompt and early treatment prevents both the lethal and nonlethal complications of the disease in all age groups The mortality rate must now be extremely low

Treatment Treatment of erysipelas should be that recommended (see Introduction) for severe hemolytic streptococcal infection The application of petrolatum two or three times a day or of cold normal salt solution to the involved skin often increases the comfort of the patient during the first two days of treatment before the infectious process subsides

The temperature returns to normal within forty-eight hours after the initiation of effective chemotherapy and the spread of the skin lesion stops abruptly Several days usually elapse before the skin returns to normal

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Peritonsillar Abscess

(Quinsy Sore Throat)

Peritonsillar abscess is a complication of hemolytic streptococcal sore throat in which suppuration extends through the capsule of the palatine tonsil into the loose connective tissue of the neck

Etiology The etiology of peritonsillar abscess is unknown Hemolytic streptococci are not regularly recovered from the purulent exudate The streptococcal infection may damage the tissues permitting invasion by other organisms It is probable that anaerobic gram negative bacilli of the Bacteroides group and anaerobic non hemolytic streptococci are involved in many cases The disease has become very uncommon since the introduction of antimicrobial therapy of tonsillitis

Symptoms and Signs The abrupt increase of soreness and swelling of the neck on one side during the course of an illness associated with sore throat is the most important symptom of peritonsillar abscess This change in the course of the illness usually is accompanied by increased fever and malaise Swallowing may become impossible the neck will bend toward the affected side and eventually it may be impossible for the patient to open his mouth

On examination the affected tonsil and anterior pillar are greatly swollen and may protrude to the midline of the throat The cervical lymph nodes on the same side are also greatly enlarged and tender Eventually a fluctuant area can be palpated by the gloved finger in the supratonsillar fossa

Complications The most important complications are those in which the suppurative process extends further into the neck and those associated with septic thrombophlebitis of the cervical veins with bacteremia and dissemination of the infection

Aspiration of purulent material from a spontaneously ruptured abscess and development of pneumonia or lung abscess may also be a hazard

Treatment The treatment should be that outlined for severe and complicated hemolytic streptococcal infections (see Introduction) The whole process will subside without drainage if therapy is instituted early If not liquefaction of the affected tissues will occur The purulent collection may rupture into the throat spontaneously or the fluctuant area may be incised through the mouth The latter procedure is preferable and is usually followed by prompt improvement

though an occasional case caused by a strain of group C has been recognized

The precise way in which the bacteria are introduced into the skin in primary facial erysipelas has not been determined Large numbers of group A streptococci are quite constantly present in the nasopharyngeal flora of patients with early erysipelas It may be that the primary infection is a nasopharyngitis from which the organism is transferred to the skin This situation prevails in sporadic streptococcal impetigo which is such a common complication of hemolytic streptococcal respiratory infection in small children

After reaching the face the streptococci may enter the skin through minute abrasions that are not recognizable after the disease is well established This hypothesis presumes that the organisms in the skin have been derived from the patient s own respiratory tract In surgical and wound erysipelas it is probable that streptococci are introduced into the traumatized areas from external sources usually the nose and throat of attendants and other patients

Epidemiology The epidemiology of facial erysipelas must be that of group A hemolytic streptococcal infection but the affected age groups are different This disease when large numbers of cases were observed in the past was rather common in infancy rare between the ages of six and thirty and was predominantly a disorder of middle age This is precisely the reverse of the age distribution of streptococcal respiratory infection There has been no explanation for this discrepancy in age distribution

Pathology Erysipelas is an acute inflammation of the skin associated with the presence of hemolytic streptococci in the lymph channels The organisms spread through these vessels to involve adjacent tissues They may be isolated easily from the advancing border of the lesion by appropriate methods

Natural History The febrile onset of erysipelas is usually abrupt and is often associated with a shaking chill A history of a preceding acute or subacute upper respiratory infection is obtained in approximately one third of adult cases and more frequently in infants

The local lesion is not infrequently minimal and may be overlooked during the first twenty four hours of illness Usually however there is a definite zone of redness and edema of the skin which can be readily discovered very early in the disease It most frequently involves the bridge of the nose in the facial form and is found around a surgical incision traumatic wound area of dermatitis or the newly severed umbilical cord in the extrafacial types of the disease

Facial erysipelas is usually self limited if no antibacterial therapy is administered Under these circumstances the temperature remains at a high level for four to ten days (mean of seven and one half days) and then falls by lysis or crisis During this interval the local process involves a large part of the face As the lesion develops and spreads from the central focus the skin is red hot edematous and glistening Blebs are frequently formed The advancing edge is sharply defined and slightly elevated Great swelling occurs when the infection involves the eyelids

The disease may involve one or both sides of the face and usually remains active and spreading until the cheeks and eyelids are affected Very often the inflammatory process does not extend over the bony prominences and is limited to the area between the mandible the malar eminence and the hair line In certain cases the ear is included but spread to the scalp and trunk is rare except in infants

Untreated erysipelas of the trunk or extremities which usually occurs in infants or persons who have undergone surgery or have been injured is a more malignant disease Large areas of skin are often involved rapidly prostration is great and death is a common event In this form of the disorder it is often possible to observe the characteristic recovery of the skin first affected while the process advances elsewhere This sequence of events also occurs in facial erysipelas but is perceived with greater difficulty Healing of the skin requires one to two weeks after the temperature has returned to normal

Diagnosis The diagnosis of erysipelas should present few difficulties after the skin lesion has become well established but may be impossible in the case in which fever precedes the signs of local infection Cellulitis of an extremity or about an operative site may resemble erysipelas as may osteomyelitis of the maxillary or frontal bones accompanying paranasal sinusitis

The demonstration of large numbers of hemolytic streptococci in the nasopharyngeal flora or in an operative or traumatic wound provides confirmatory evidence in the diagnosis of erysipelas Leukocytosis is regularly present in this disease

sensitivity is concerned leaves many questions unanswered However there is much to suggest that an antigen antibody reaction involving one or more of the many products of the hemolytic streptococcus may play a role in the pathogenesis of the disease

It must be emphasized that only a small percentage of persons who suffer from streptococcal sore throat or scarlet fever subsequently develop rheumatic fever As virtually all known serological types of group A streptococci appear to be capable of inducing rheumatic fever it is suggested that the relatively infrequent occurrence of the disease is dependent upon host factors rather than on differences in the organism This point of view is supported by the fact that patients known to have had previous attacks of rheumatic fever show a greatly increased incidence of the disease following streptococcal infections

It is the opinion of some clinicians that attacks of rheumatic fever may occasionally be initiated by stimuli other than a streptococcal infection This possibility is not well established since most of the reported cases of this type have not been studied with respect to the possible occurrence of recent streptococcal disease In any event from the practical point of view it can be stated that if such exceptions occur they must be extremely rare

Incidence and Epidemiology Rheumatic fever is primarily a disease of childhood with a peak incidence between the ages of five and fifteen years but it is by no means limited to this group The disease is rare in infants and in adult life it becomes progressively less common with advancing age It seems probable that its predominance in childhood is directly related to the high incidence of streptococcal infections during this period of life When unusual conditions result in an increase in the attack rate of streptococcal disease in adult populations as has occurred in the case of certain military establishments the incidence of rheumatic fever appears to be comparable with that seen in childhood

For many reasons there are no reliable figures which give an accurate picture of the general incidence of rheumatic fever The disease is not reportable in most communities and even if it were the difficulties of diagnosis would seriously affect the accuracy of the data Special surveys in individual communities have yielded figures for the incidence which vary over a wide range from 0 1 per cent to more than 5 per cent As a result of recent studies somewhat more consistent figures are available for the frequency with which rheumatic fever occurs following streptococcal infections In a number of epidemics of streptococcal disease in different localities of the United States the incidence of rheumatic fever was approximately 3 per cent While the attack rate may be appreciably greater or smaller in certain epidemics this figure provides a reasonable index of the risk of rheumatic fever in untreated streptococcal infections In contrast to these findings the incidence of recurrences of the disease in known rheumatic subjects has been reported to be as high as 30 to 50 per cent following streptococcal infection

Despite the inadequacy of statistical information it is generally believed that the incidence of rheumatic fever like that of streptococcal sore throat and scarlet fever has been decreasing for several years It is possible that the rate of decrease has recently been accelerated by the wide use of antimicrobial drugs However rheumatic fever remains one of the most important of the serious diseases of childhood

It is evident from the close relationship between the two diseases that the epidemiology of rheumatic fever may be considered as a special branch of the epidemiology of streptococcal infections The parallelism between the two diseases is illustrated by the geographical and seasonal variations in their occurrence In the United States both have their peak incidence during the late winter and early spring and they are encountered with considerably greater frequency in the northern than in the southern states In individual epidemics the peak incidence of streptococcal disease precedes that of rheumatic fever by one to three weeks as would be expected on the basis of the time interval separating them in individual cases of rheumatic fever

Rheumatic fever appears to be more common among families in the lower economic group The effect of poverty is probably dependent upon such factors as malnutrition overcrowding and substandard housing which in turn lead to an increased incidence of streptococcal disease There is in addition evidence for an hereditary predisposition to the disease and it is common to obtain a family history of rheumatic fever as well as to encounter multiple cases among the siblings of a single family It has not been shown that this hereditary predisposition is associated with an increased susceptibility to streptococcal infection

Morbid Anatomy Histological examina

Hemolytic Streptococcal Pneumonia

Group A hemolytic streptococci were once responsible for 3 to 5 per cent of cases of bacterial pneumonia but this form of the disease is now rarely seen It usually appears as a complication of influenza or other viral respiratory infection or in persons with underlying pulmonary disease It is almost never observed as a sequel to streptococcal tonsillitis and pharyngitis or scarlet fever

The pneumonic process is lobular in distribution in the lung Empyema develops in 30 to 40 per cent of untreated cases It is present early in the illness and is characterized by the formation of large amounts of thin fluid Ten to 15 per cent of all cases are bacteremic

The demonstration of large numbers of hemolytic streptococci in the sputum by cultural methods or the isolation of these organisms from the blood or pleural fluid is required for diagnosis

Little information is available as to the results of the treatment of hemolytic streptococcal pneumonia with antimicrobial agents The regimen employed should be that for severe streptococcal infections (see Introduction) and the results should be good with a reduction in mortality from the 15 per cent rate attained with sulfonamides

It has been demonstrated in a few cases that purulent contents of the empyema cavity may be readily sterilized by the combined intrapleural and parenteral administration of penicillin In spite of this fluid may continue to form and a long period of time may be required for it to disappear even with frequent aspirations Recovery is usually facilitated by the closed insertion of a small tube permitting free drainage of the pleural space

Pneumonia is certainly caused by other streptococci including those nonhemolytic varieties normally present in the upper respiratory tract The latter may be aspirated and may thus produce disease especially in persons with underlying structural abnormalities of the lung This type of illness has been little studied and is difficult to recognize clinically

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Rheumatic Fever

Definition Rheumatic fever is a febrile disease which occurs as a delayed sequel of infections with group A hemolytic streptococci It is characterized by the occurrence of multiple focal inflammatory lesions in many parts of the body notably in the heart blood vessels and joints Among the diverse manifestations of the disease those with the most serious clinical implications are concerned with involvement of the heart Thus the name rheumatic fever which emphasizes the occurrence of inflammation of the joints fails to convey anything with regard to the manifestations of primary importance

Etiology In recent decades it has become increasingly clear as the result of several independent lines of evidence that group A hemolytic streptococci are intimately concerned in the pathogenesis of rheumatic fever Numerous clinical and epidemiological studies pointed to a relationship between streptococcal sore throat and rheumatic fever These observations have been strongly supported by an increasing body of immunological data which demonstrate the occurrence of antibodies to streptococcal antigens in the course of rheumatic fever Indirect confirmation is provided by the fact that the disease can be prevented by the antimicrobial therapy or prophylaxis of streptococcal infections

While the importance of streptococcal infections in rheumatic fever appears to be established the mechanism by which the hemolytic streptococci initiate the disease process remains obscure The disease is not comparable to those bacterial infections in which the organism is readily demonstrable in the lesions The symptoms of rheumatic fever first become manifest after an interval of several days to several weeks following the acute streptococcal infection at a time when hemolytic streptococci may no longer be recoverable on culture of the nose and throat Even when streptococci are still present at the time of onset of rheumatic fever elimination of the organisms with penicillin appears to have no striking influence on the manifestations or the course of the illness It is concluded therefore that the organism exerts its effect through some indirect process rather than by the continued presence of viable streptococci in the tissues of the host No completely satisfactory hypothesis has been advanced regarding the mechanism of this process and the current theory that some form of hyper

organ but appears to involve the mesenchymatous connective tissue so that numerous areas of the body may be affected The major symptoms include fever pain arising from inflammation of the joints various manifestations of involvement of the heart and pericardium abdominal pain skin changes and chorea The general symptoms of anorexia loss of weight weakness and fatigability are almost invariably present

The onset of the disease may be insidious and gradual or acute The relationship to a preceding streptococcal infection is not always clear since the infection can be so mild as to escape notice completely During the interval between the streptococcal infection and the onset of rheumatic fever usually a period of one to four weeks the patient may appear to be entirely well and be able to engage in his normal activity On some occasions however laboratory examinations will reveal evidence of disease activity during this so called latent interval

The most common type of onset of rheumatic fever is characterized by the sudden occurrence of fever and joint pain While the fever may be high and sustained in severe cases it is more frequently moderate and often low grade The patient may complain of sore throat even though examination reveals minimal evidence of acute inflammation and significant bacterial infection may not be demonstrable Epistaxis occurs commonly both at the onset and throughout the acute stage of the disease and in some cases results in serious loss of blood

Joint Involvement The manifestations of *polyarthritis* vary from vague discomfort in the extremities to the exquisite pain associated with acutely inflamed and swollen joints In the former instance there is little or no objective evidence to confirm the presence of inflammation of the articular surfaces On the other hand in the case of the severely involved joint the skin shows local redness and heat the joint is markedly swollen with obliteration of the normal configuration and fluid is obviously present within the joint cavity Passive or active movement of the joint is extremely painful The fluid in joints of this type is turbid and contains inflammatory leukocytes but is sterile on bacteriologic culture A single joint may be affected or most of the large joints in the body may be involved at one time Characteristically however the arthritis is migratory in nature and as the pain and swelling subsides in one area others become involved The large joints of the extremities are most frequently affected but no area appears to be immune and one may find arthritis of the hands feet spine or of such joints as the sternoclavicular and temporomandibular

There appears to be some variation with age in the pattern of joint involvement most frequently encountered In the youngest age group in which rheumatic fever is regularly recognized from four to six years frank arthritis is a less common feature of the disease These small children may complain of mild joint pains or merely vaguely localized aching of the extremities This type of complaint at one time discounted as "growing pains" is usually associated with only low grade fever but despite the benign character of the overt symptomatology can be associated with serious involvement of the heart Rheumatic fever in older children and young adults is more often associated with the classic migratory polyarthritis although even in this group the manifestations are diverse It should be emphasized that rheumatic fever can occur without any evidence of joint involvement whatever

Cardiac Involvement In the course of acute rheumatic fever the patient may have little in the way of symptoms referable to cardiac involvement and it is usually necessary to depend on clinical roentgenographic and electrocardiographic examinations to determine the extent and seriousness of this manifestation of the disease Since all of the major anatomical divisions of the heart are subject to the disease the manifestations vary depending on the relative concentration of lesions in the different areas of the heart *Myocarditis* and *pericarditis* are responsible for most of the abnormal findings during the acute stage of the disease and the presence of *endocarditis* is not readily demonstrated even in those cases in which the subsequent course of events makes it obvious that endocarditis was extensive Endocarditis involving the leaflets of the valves is responsible for the scarring and distortion which lead to permanent valvular heart disease

Precordial pain or discomfort is one symptom which is often encountered and it is usually a reflection of myocardial disease rather than of pericarditis The patient may also complain of palpitation or unpleasant consciousness of the rapid action of the heart If the disease is sufficiently extensive to cause serious impairment of the function of the heart the usual symp

tion of the tissues in rheumatic fever reveals multiple areas of focal inflammation which are disseminated widely throughout the body with special predilection for connective tissue The basis for the focal nature of the lesions is not determined although it is known that the small blood vessels are extensively involved The detailed microscopic appearance of the inflammatory lesion varies with its location and the most characteristic and specific pattern is found in the myocardial Aschoff body This lesion when present in its classic form is generally considered to be *pathognomonic of rheumatic fever* In many areas the inflammatory lesion is accompanied by an alteration in the staining properties of the ground substance of the connective tissue This change is described as fibrinoid degeneration of collagen" but its chemical basis has not been established Valvulitis which leads to the most serious permanent damage is characterized during the acute stage by interstitial inflammation and the appearance of minute vegetations on the surface of the valve near its margin

Pathological Physiology and Chemistry In many respects the alterations in chemical constitution of the body which occur in the course of rheumatic fever are similar to those encountered in other acute febrile diseases This is particularly true of the numerous changes in the peripheral blood It has been demonstrated by chemical and electrophoretic analysis that increases in concentration occur in several of the protein fractions of the blood including fibrinogen and alpha and gamma globulins These increases in protein concentration are accompanied by a variety of changes in the properties of the blood which are dependent upon an increased concentration of certain individual components Thus *the erythrocyte sedimentation rate* is markedly elevated and abnormally high concentrations of such constituents as complement mucoprotein and nonspecific hyaluronidase inhibitor are found In addition new substances appear which are not normally present in blood These latter are exemplified by the so called C reactive protein and by substances which are bactericidal for a variety of microorganisms

It should be emphasized that these changes in constituents of the blood are not limited to rheumatic fever but are found in numerous disease states Somewhat more specific alterations occur as the result of the appearance of antibodies directed against various components of the hemolytic streptococcus These antibodies are responsible for at least part of the observed increase in gamma globulin concentration They have been demonstrated for several extracellular products of the streptococcal cell such as streptolysin O streptokinase streptococcal hyaluronidase and desoxyribonuclease as well as for cellular components such as the type specific M protein The anti streptococcal antibodies usually become detectable in the blood about one week after a streptococcal infection and increase in titer for three or four weeks Because of the time relationships between precursory streptococcal infection and rheumatic fever the antibody titers are generally still increasing at the time of appearance of rheumatic symptoms The level of circulating body declines gradually after the peak has been reached

Numerous comparisons have been made in recent years between the antibody response shown by patients with uncomplicated streptococcal infections and those who develop rheumatic fever as a late complication It has been found that while there is no consistent qualitative difference between the two groups the proportion of rheumatic patients who develop significant antibody responses to a given antigen is higher than that of patients with uncomplicated streptococcal disease In individual epidemics of streptococcal infection the mean antibody response of those who develop rheumatic fever is consistently greater than the mean response of the great majority who suffer no complications The significance of this immunological hyperreactivity of the rheumatic subject in relation to the pathogenesis of the disease has not been established

Gross changes in the respiratory and cardiac physiology during acute rheumatic fever are dependent to a large extent on *the degree of involvement of the heart* When myocarditis is extensive cardiac failure may intervene early in the disease and the alterations dependent on the acute febrile nature of rheumatic fever are complicated by those arising from cardiac decompensation More subtle disturbances in cardiac physiology frequently result from interference with the conduction system so that alterations in rhythm and various *types of heart block are encountered*

Symptoms and Signs The symptoms of rheumatic fever are diverse and cover an extremely wide range both with respect to the variety of manifestations and the degree of intensity with which they occur In part this is a reflection of the fact that it is not a disease of a single circumscribed

Pleurisy which at one time occurred quite frequently in rheumatic fever appears to be an unusual manifestation of the disease at the present time

Abdominal pain unassociated with arthralgia or arthritis may be the presenting complaint at the time of onset of the disease This symptom is most commonly encountered in children and although the pain and associated tenderness are usually not well localized their significance is frequently misinterpreted In some instances bouts of abdominal discomfort or pain persist throughout the period of activity of the disease The precise origin of these abdominal symptoms has not been established

The characteristic manifestation of *skin involvement* in acute rheumatic fever occurring in about one fourth of childhood cases is a multiform type of erythema commonly designated as *erythema marginatum* or *circinatum* It consists of roughly circular lesions which may be distributed over the extremities trunk and sometimes the face and which spread centrifugally leaving a clear center The lesions tend to coalesce so that although individual areas are iris like the larger areas are serpiginous in outline The erythema blanches on pressure and may be quite evanescent disappearing and later reappearing at the same sites The lesions are usually not elevated although in some cases a slight papular quality may be detected In the vast majority of instances the rash occasions no discomfort but well authenticated cases have occurred in which itching has been a troublesome factor Erythema marginatum is not pathognomonic of rheumatic fever and similar rashes may occur in association with other diseases Rarely purpura is seen in rheumatic fever

Erythema nodosum is another skin disorder which appears to be a manifestation of the acute rheumatic process However it is not nearly so frequent in occurrence as erythema marginatum and often occurs when other evidence of rheumatic disease is equivocal or lacking It would appear that only a portion of the cases of erythema nodosum are referable to rheumatic fever The dull red nodular lesions occur most frequently on the extensor surfaces of the extremities and vary in size from less than one centimeter to many centimeters in diameter They are extremely tender on pressure and the pain is aggravated by movement of the extremities

Subcutaneous rheumatic nodules represent *a quite different type of lesion* These are firm insensitive nodules which occur over the bony prominences of the various joints and tendons of the extremities the spine and the back of the head They appear to be loosely attached to the underlying tissue and the skin is freely movable over them Increasing the tension of the skin by flexion of the joints makes the nodules more readily apparent and it is often necessary to use this procedure in order to detect the presence of small nodules When nodules are numerous there is a tendency for them to be symmetrical in distribution Subcutaneous nodules are most frequently encountered in the more severe cases of rheumatic fever with serious cardiac involvement In part this may be due to the fact that the presence of nodules is much more readily detectable when there is loss of subcutaneous tissue as the result of chronic rheumatic disease Thus patients with nodules usually also show marked evidence of wasting and loss of weight

Chorea may occur as a manifestation of rheumatic fever either alone or in combination with other symptoms of the disease While there is some question whether all cases of pure chorea without other evidence of rheumatic disease *are related to* rheumatic fever there is no doubt that it occurs as the sole manifestation of the disease in some cases When chorea is unassociated with other rheumatic symptoms fever and other systemic changes reflected by such tests as the erythrocyte sedimentation rate are usually absent It would appear that when rheumatic involvement is confined to the central nervous system the characteristic general systemic response is reduced to a minimum

The onset of chorea is usually insidious and the parents of a child with chorea may first note only increased awkwardness and a tendency to spill food or drop objects which is attributed to carelessness Even the appearance of involuntary purposeless movements of the extremities may be discounted as nervousness However with further progression of the disease the irregular and uncontrollable movements become obvious These may be extensive and involve not only the hands feet arms and legs but the tongue and facial muscles The severity may range from cases in which the movements are detectable only after close observation to those in which violent continual activity totally incapacitates the patient and necessitates protection from self injury In moderate cases it is *common for chorea* to interfere with

toms of cardiac failure will be superim*posed on those of the acute rheumatic* process

The findings on physical examination reflect the same wide variation in severity of disease that the symptoms display In the simple relatively benign case there may be nothing more than a tachycardia which cannot be interpreted as unequivocal evidence of cardiac involvement In the more severe cases one may detect generalized cardiac enlargement and in addition to the rapid heart rate the heart sounds in the apical area may be muffled indistinct *and of poor muscular quality The latter* findings are often associated with a diffuse precordial impulse The second sound in the pulmonic area is commonly greatly accentuated in comparison with the second aortic sound Gallop rhythm may occur and is usually an indication of serious myocardial disease

The cardiac murmurs which appear during the acute phase of initial attacks of rheumatic fever are most frequently blowing systolic murmurs best heard in the apical area and are considered to be caused by *dilatation of the valve rings as a result* of general dilatation of the heart Less commonly soft diastolic murmurs will be heard along the left sternal border in the third and fourth interspaces It is difficult to determine whether inflammation of the valve leaflets contributes significantly to these murmurs As the murmurs may disappear permanently on recovery their final significance cannot be determined except by repeated examination during and after convalescence

When the pericardial component of carditis becomes extensive the classic to and fro friction rub will be heard over the precordium This physical sign may be of brief duration or may persist for days and it will sometimes disappear with the accumulation of fluid in the pericardial sac

Disturbances in the conduction system of the heart are best detected by the use of electrocardiography Occasionally however irregularities in the rhythm resulting from second degree heart block can be recognized clinically The most common manifestation of interference with conduction in rheumatic fever is prolongation of *the P R interval* in the electrocardiogram reflecting a delay in transmission of the excitation wave from auricle to ventricle The interference with conduction may be increased to the point where dropped beats result and the rhythm may assume a regular pattern with the beats occurring in couplets or triplets Complete auriculoventricular dissociation may also occur with the ventricles assuming a rhythm independent of that of the auricles More rarely auricular fibrillation will make its first appearance during acute rheumatic fever In addition to these conduction anomalies the electrocardiogram may show T wave abnormalities most commonly inversion of the wave in one or more leads In the presence of pericarditis elevation of the S T segment may occur in the acute phase with subsequent alterations in the configuration of the T wave which simulate those seen in coronary disease

The roentgenographic findings may be unremarkable in acute rheumatic fever unless the myocarditis is sufficiently severe to give rise to dilatation of the chambers of the heart When dilatation occurs generalized enlargement of the heart is apparent on roentgenography and changes in size may occur quite rapidly as a result of changes in the activity of the disease process

The foregoing description of the findings referable to cardiac involvement is applica*ble to those cases of acute rheumatic* fever in which previous damage to the heart has not occurred However since rheumatic fever is characteristically a recurrent disease it is common to encounter the acute disease in patients with well-established rheumatic valvular disease This may occur even in the absence of a *history* of previous attacks of rheumatic fever In cases of this type the manifestations of acute rheumatic carditis are superimposed on those of chronic valvular disease The character of established murmurs may be modified by the acute myocardial disease and the reserve of the heart is diminished so that cardiac failure is a greater threat If the status of the patient prior to the onset of the acute attack is unknown it is frequently difficult to distinguish between the effects of the acute process and those of chronic disease until convalescence is complete

Miscellaneous Clinical Manifestations Involvement of the *lung* in rheumatic fever leads to a type of pneumonitis which is very difficult to detect clinically The existence of rheumatic pneumonia was first established by the pathological examination of postmortem material It is most common in the severe and fulminating cases in which any clinical or roentgenographic evidence of a pneumonic process may be obscured by acute congestion of the lungs resulting from cardiac failure

result does not eliminate the possibility of a recent streptococcal infection Secondly patients with nonrheumatic disease may also show evidence of an antibody response to a streptococcal infection which is unrelated to their presenting illness particularly during periods of high incidence of streptococcal disease Despite these limitations the antibody tests are valuable additions to the total collection of facts which must be evaluated in reaching a diagnosis

Among these tests the most widely employed and the most practical for general use is the measurement of antibody against streptolysin O The *antistreptolysin O titer* is significantly elevated (above 150 units per ml) in 85 per cent or more of rheumatic fever patients The significance of the antibody information can be increased by carrying out determinations of more than one antibody and in some cases it is helpful if facilities are available to measure antistreptokinase and antihyaluronidase in addition to antistreptolysin O The absence of a significant elevation in titer of any of the three antibodies would render the diagnosis of rheumatic fever doubtful

Other laboratory tests used in rheumatic fever such as the erythrocyte sedimentation rate offer relatively little assistance in diagnosis and are of value chiefly in following the activity of the disease process once the diagnosis has been established

Differential Diagnosis Because of the protean manifestations of rheumatic fever a wide variety of clinical conditions must be considered in differential diagnosis Low grade febrile illnesses of undetermined origin frequently present the most difficult diagnostic problems The possibility that illnesses of this type represent subclinical or smouldering rheumatic activity must be considered and this is especially true when the common symptom of pain or discomfort in the extremities is present The problem becomes even more pressing when low grade febrile disease occurs in a person known to have previously suffered one or more attacks of rheumatic fever In this instance the marked tendency of rheumatic fever to recur increases the likelihood that the obscure disorder represents rheumatic activity The problem can be resolved only by close observation and careful study to uncover additional evidence for or against the diagnosis *Chronic upper respiratory disease chronic tonsillitis brucellosis* and *infectious mononucleosis* are among the diseases which must be considered in this connection

Intercurrent respiratory disease or other febrile illness in children with previously undiagnosed congenital heart disease may be confused with rheumatic fever if cardiac murmurs arising from the congenital defect are misinterpreted as rheumatic in origin Thorough study of the cardiac abnormality will usually reveal its nature

Acute septic arthritis for example streptococcal or gonococcal arthritis will simulate rheumatic arthritis especially in the early stages when the inflammation of the joint is indistinguishable from that seen in the severely involved joint in rheumatic fever As the disease progresses the manifestations of the septic joint are more severe than observed in rheumatic fever and there is a marked tendency for inflammation and edema to extend into the soft tissues at some distance from the joint The diagnosis can be readily established by removal of fluid from the involved joint for bacteriological examination Among other acute bacterial infections *acute staphylococcal bacteremia* may also simulate rheumatic fever in its early stages since wide dissemination of the organisms may lead to transient symptoms of multiple joint involvement as well as to pleurisy and pericarditis In addition before the pain of *staphylococcal osteomyelitis* becomes sharply localized this disease may be confused with rheumatic fever When joint involvement occurs in *serum disease* the clinical picture is similar to that of certain cases of rheumatic fever

Chronic rheumatoid arthritis especially in the early months of the disease before the chronicity of the process and the extensive nature of the articular damage become apparent must be distinguished from rheumatic fever Although cardiac signs and symptoms and other stigmata of rheumatic fever are usually absent continued observation for many weeks is sometimes required before the diagnosis can be eliminated as a possibility Similarly the arthritis due to *gout* must be considered in the differential diagnosis in the adult Among rare disease states certain cases of *periarteritis nodosa* and *disseminated lupus erythematosus* may be difficult to differentiate from rheumatic fever in early stages of the disease

Subacute bacterial endocarditis occurs most commonly in persons with valves previously damaged by rheumatic fever and it often presents a clinical picture which is not readily distinguishable from a rheumatic recurrence Vague pains in the extremities are more common than overt arthritis but these symptoms together

all coordinated operations such as writing and eating In some cases chorea may be limited to one side of the body The disease appears to affect females somewhat more frequently than males although this sex preponderance probably has been over stressed in the past

Laboratory Findings *Hematology* Alterations in the leukocytes during acute rheumatic fever are similar to those encountered in an acute streptococcal infection A definite leukocytosis is usually encountered with total leukocyte counts ranging from 12 000 to 24 000 per cu mm This is associated with an increase in the percentage of polymorphonuclear elements

A moderate degree of anemia is found in the majority of cases This anemia is usually normocytic in type with proportional decreases in the hemoglobin concentration and erythrocyte count It is similar to the anemia encountered in infections and to some extent may have its origin in the precursory streptococcal infection However the anemia does not tend to improve while the rheumatic process remains active In many cases the anemia is superimposed on a pre existing nutritional anemia and may be more severe in degree The most severe anemias encountered in rheumatic fever are those associated with loss of blood resulting from epistaxis

Urinary Findings A high percentage of patients with rheumatic fever show the presence of some proteinuria and an increase in the numbers of formed elements in the urine during the acute phase of the disease However the changes are rarely as marked as those characteristically encountered in acute hemorrhagic nephritis and it is uncommon to find the two diseases simultaneously in the same patient despite the fact that both follow infection with hemolytic streptococci

Diagnosis In the classic case of rheumatic fever diagnosis presents no problems Thus when one is confronted with a patient who develops fever migratory polyarthritis unequivocal evidence of carditis and erythema marginatum three weeks following a severe sore throat there is little doubt concerning the correctness of the diagnosis This type of case is relatively unusual however and it is more often necessary to rely on careful evaluation of all available lines of evidence including history symptoms signs and laboratory data Criteria for diagnosis of rheumatic fever have been suggested on the basis of the combination of major and minor manifestations of the disease which should be considered as the minimal requirement but in practice it is not possible to adhere rigidly to any formula for diagnosis Not only do the symptoms of certain other diseases simulate those of rheumatic fever but the overt manifestations of rheumatic fever may be so atypical or minimal as to mislead the diagnostician In this connection it is pertinent to note that in routine examination of school populations cases of unequivocal rheumatic heart disease with no history of an attack of acute rheumatic fever are frequently encountered and it must be assumed that the acute disease occurred as an undiagnosed illness When one considers the mildness or the bizarre character of certain cases of known rheumatic fever it is not difficult to understand how the disease frequently escapes recognition

It is important to inquire carefully for family history of rheumatic fever and for past illnesses that may have represented previous attacks of the disease The history of sore throat in the weeks prior to the onset of the disease may be helpful as an indication of a precursory streptococcal infection However it should be noted that a negative history in this regard is inconclusive since mild or relatively asymptomatic infections may be disregarded or forgotten by the patient Evaluation of the various symptoms presented by the patient often requires close questioning concerning their exact nature and timing Arthralgia and vague pain or discomfort in the extremities especially in the young child must be given serious consideration as possible manifestations of the disease In the doubtful case in which objective joint involvement is lacking physical examination centers on the attempt to determine whether carditis is present When recurrence of the disease is suspected in a known rheumatic patient it is necessary to distinguish between the manifestations of acute carditis and those of established valvular disease

The difficulties involved in recognition of the disease are increased by the fact that there is no specific diagnostic laboratory test The laboratory procedures that provide the most assistance in diagnosis are those concerned with the measurement of antibodies to streptococcal antigens but the most that can be expected of these tests is that they will supply evidence of a recent streptococcal infection The limitations of this type of evidence are twofold In the first place all persons do not show significant antibody responses to a single streptococcal antigen and consequently a negative

attack of the disease and the danger appears to diminish with advancing age However there is no age at which the rheumatic subject can be considered free from the threat of recurrence following an infection with hemolytic streptococci

The predisposition to bacterial endocarditis is another factor which affects the long term prognosis in rheumatic fever Prior to the introduction of effective antimicrobial therapy endocarditis was a uniformly fatal disease and second only to congestive heart failure as a cause of death among rheumatic subjects The present success in curing a high percentage of cases of endocarditis does not completely remove the serious prognostic implications of the disease however since the bacterial infection frequently results in further damage to the affected valves before it is eliminated

As a result of the widespread use of mitral commissurotomy for surgical correction of stenotic mitral valves biopsy fragments of the auricular appendage have become available for pathological examination It has been found that Aschoff bodies are present in the auricular tissue of at least 40 per cent of patients coming to operation even though care has been taken to eliminate all patients with clinical or laboratory evidence of rheumatic activity This finding again raises the question of whether rheumatic activity continues at a subclinical level for many years in a high percentage of cases However at the present time the significance of the Aschoff body is not sufficiently well established to draw final conclusions concerning the persistence of rheumatic activity on the basis of this finding alone

Treatment During the acute febrile phase of rheumatic fever general care is like that of other febrile diseases with emphasis on maintenance of an adequate fluid intake Conservative management of the disease requires that bed rest be continued as long as evidence of the disease activity persists Because of the prolonged nature of the disease in many cases this requirement poses a special problem in the maintenance of the patients morale Therapeutic measures will usually eliminate all symptoms of the disease and consequently it is difficult to reconcile the patient to the necessity of remaining in bed Planned recreation and occupational therapy adjusted to the interests and capabilities of the patient are essential at the same time it is advisable to attempt education concerning the nature of this disease Education must be continued into the period of convalescence since the concept of the variability of the outcome of rheumatic fever is often poorly grasped and one must guard against both unnecessary anxiety and unfounded complacency It is possible for a patient without significant residual heart damage to become psychologically crippled by exaggerated fear of the disease and on the other hand an individual with serious cardiac involvement may discount the dangers and attempt to carry on all the activities of a normal healthy person In childhood rheumatic fever education of the parents assumes first importance

The necessity for prolonged bed rest has been challenged by some clinicians and it must be admitted that proof of its value has not been established by controlled experiment However it has been repeatedly observed that the most unfavorable results in rheumatic fever occur when intermittent or semi ambulatory care is practiced It is permissible to modify the regimen by allowing bathroom privileges and exceptions to the rule that bed rest must be continued until all evidence of disease activity is gone may occasionally be made when a minor manifestation of the disease persists in the absence of all other symptoms or signs Thus it is difficult to justify keeping a patient in bed solely because of the presence of erythema marginatum

After rheumatic fever is first diagnosed a course of penicillin should be given to eliminate hemolytic streptococci This is advisable even if bacteriological examination yields negative throat cultures for streptococci since the organisms may remain in inaccessible areas It is preferable to administer the penicillin parenterally and 300 000 units of procaine penicillin once a day in children and twice a day in adults for seven to ten days represents an effective dose A single dose of 1 200 000 units of the long acting benzathine penicillin may also be used After completion of the therapeutic course of penicillin it is important to provide continuous protection from reinfection with hemolytic streptococci both by attempting to prevent exposure and by instituting a program of prophylactic drug treatment according to one of the regimens discussed below

The *symptomatic treatment* of rheumatic fever at the present time is generally carried out with salicylates or with one of the hormone products cortisone prednisone or corticotropin The relative merits of these agents in controlling the various manifestations of the disease are still under investigation and it is not yet possible to define

with fever and debility in a known rheumatic individual are sufficient to suggest a rheumatic recurrence The difficulties are increased by the fact that in some cases *it is not possible to recover the offending* organism in blood culture The characteristic petechiae and painful septic emboli of endocarditis are helpful in differential diagnosis (See section on Bacterial Endocarditis in Diseases of the Cardiovascular System)

When abdominal pain is the initial symptom in acute rheumatic fever the illness is frequently mistaken for *appendicitis* and all too frequently an unnecessary appendectomy is performed The highly localizing signs characteristic of classic appendicitis are not found but because of the fact that appendicitis in children is often atypical the lack of these findings is not conclusive *However if a brief period for observation* is allowed in doubtful cases other manifestations of rheumatic fever may become apparent

The so-called *benign idiopathic pericarditis* which is apparently not rheumatic in origin is indistinguishable in the acute phase from those cases of rheumatic fever in which pericarditis is the major detectable manifestation The diagnosis of idiopathic pericarditis is dependent primarily on elimination of other possibilities and on the subsequent course of the disease which is characterized by complete recovery without residual damage Thus the final conclusion is often reached only in retrospect and must remain somewhat uncertain since rheumatic pericarditis with minimal involvement of the myocardium and endocardium could conceivably behave in a similar fashion

Acute aleukemic leukemia may occasionally mimic rheumatic fever closely with fever and extremity pain The nature of the disease may not be suspected until the failure of therapeutic measures suggests the possibility Examination of the peripheral blood and the bone marrow will serve to suggest the correct diagnosis *Sickle cell anemia* represents a second disease of the blood which can simulate rheumatic fever It is advisable to examine the blood for sickling in all cases of suspected rheumatic fever in members of the Negro race

When uncertainty concerning the diagnosis exists it is often useful to employ a therapeutic test with salicylates The rapidity with which the symptoms of rheumatic fever are controlled by these drugs in many cases is in sharp contrast to its lack of effect in most of the diseases that cause confusion in the diagnosis

Prognosis The course of rheumatic fever does not follow any single well defined pattern *Some patients who appear quite ill at* the onset of the disease become symptom free in a few days and proceed to rapid and complete recovery so that the total duration of the illness is not longer than three to four weeks *In contrast to this type of* illness fulminating attacks may be so overwhelming that death occurs early in the acute phase At the other extreme there are patients who show persisting evidence of rheumatic activity for many months or perhaps years Any of the various symptoms of the disease may occur during the course of this protracted form of the disease In some instances the subacute and chronic type of rheumatic fever is characterized by recurring cycles of activity with intervening periods of relative freedom from symptoms The importance of these characteristics of the disease from the point of view of prognosis lies in the fact that the course which the disease will follow is totally unpredictable and there is nothing in its pattern during the early stages which can be relied upon to indicate the probable duration of the illness or the likelihood of the appearance of permanent cardiac damage

Death in the acute phase of the first attack is rare but the incidence of fatality increases in recurrences of the disease in which the acute process is superimposed on permanent cardiac damage resulting from previous bouts of rheumatic fever Cardiac failure appears to be the immediate cause of death in these patients The clinical impression that the severity of rheumatic fever has tended to decline in recent decades is supported by figures indicating that the fatality rate has decreased

The long term prognosis is dependent primarily on the nature and degree of cardiac involvement Extensive malformation of one or more of the valves leading to serious interference with the efficient functioning of the heart greatly decreases the life expectancy of the patient Follow up studies on large groups of rheumatic patients have shown that the majority of those with severe cardiac involvement as *indicated by marked enlargement* of the heart or congestive failure succumb within ten years The prognosis is also affected by the fact that a new attack of rheumatic fever may contribute further damage Recurrences of the disease are most frequent in the first five years *following the initial*

Secondly since the hormones may completely suppress the overt manifestations of bacterial infections it is important to give suitable *antimicrobial therapy* during long continued hormone administration Penicillin can be used for this purpose at dosage levels recommended for prophylaxis of streptococcal infections *Theoretically* one of the broad spectrum drugs such as the tetracyclines would provide protection against a wider variety of infections but their effectiveness in patients receiving hormone therapy is less well established

Other drugs such as aminopyrine hydroxyphenylcinchoninic acid and gentisate have been employed for symptomatic control of rheumatic fever but at the present time salicylates and the hormones appear to be the drugs of choice

When cardiac failure supervenes in the course of acute rheumatic fever the general measures employed for the treatment of congestive failure must be added to those for management of the acute disease Digitalis should be administered according to the dosage schedule outlined in the chapter on valvular heart disease

Duration of Therapy The difficult problem of determining how long therapy should be maintained is the same regardless of the agent employed Since the various changes in the blood revert to normal under suppressive therapy there is no laboratory test which serves as a reliable guide to the persistence of the active rheumatic process The best that can be done once the general improvement of the patient suggests that recovery may have occurred is to withdraw the therapeutic agent *gradually and to observe carefully for the* return of symptoms or signs of rheumatic fever If unmistakable signs of severe activity reappear there is no alternative but to reinstitute therapy In this connection it is important to differentiate between a true recrudescence of rheumatic activity and the so called *rebound phenomenon* The latter phenomenon occurs to some degree in a high percentage of patients upon withdrawal of therapy and is a self limited episode characterized by the return of certain manifestations of the disease Thus there may be a change in the laboratory tests specifically some elevation in the sedimentation rate and reappearance of C reactive protein in the blood and on some occasions symptoms such as low grade fever or arthralgia may occur Since these mild manifestations disappear spontaneously in one to three weeks it is unnecessary to resume therapy However when unmistakable evidence of carditis recurs it is not advisable to withhold treatment regardless of the mildness of the symptoms

Prophylaxis *Prevention of Recurrence in a Rheumatic Subject* The prevention of recurrences of rheumatic fever depends on the prevention of streptococcal infections and every rheumatic patient should receive continuous prophylactic therapy through the school age and for at least five years following the last attack of the disease Because streptococcal infections can occur at any age prophylaxis should probably be continued indefinitely in all patients with significant heart disease The most practicable regimens involve the use of sulfadiazine or oral penicillin The dose of sulfadiazine is 0 5 gm for children under 60 pounds and 1 0 gm for older children and adults given once daily Because of the more rapid elimination of penicillin it is advisable to give this drug twice daily in doses of 100 000 to 200 000 units Oral penicillin should be given on an empty stomach preferably before breakfast and at bedtime An alternative method of prophylaxis is the intramuscular injection of 1 200 000 units of benzathine penicillin every four weeks This is especially useful whenever the self administration of oral drug is irregular or unreliable

Prevention of Rheumatic Fever in a Nonrheumatic Subject In addition to this prophylactic effect of antimicrobial drugs it has been shown that prompt and intensive penicillin treatment of established streptococcal infections greatly reduces the risk of the subsequent development of rheumatic fever (see Introduction to Streptococcal Infections) This fact stresses the importance of accurate and early diagnosis of streptococcal disease in all patients regardless of whether there is previous history of rheumatic fever

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an order of preference The opinion is widely held that the hormones are able to bring about more rapid control of the symptoms especially the manifestation of carditis but it is clear that patients vary in their response to the several drugs so that even this generalization has its limitations An important practical consideration in therapy is that both salicylates and the hormones suppress the overt manifestations of rheumatic fever without eliminating the underlying disease process Thus they cannot be considered as therapeutic agents in the same sense that an antimicrobial drug is a therapeutic agent in bacterial infections

When the antirheumatic drugs are given in adequate dosage not only do the signs and symptoms of the disease tend to disappear but the changes in the blood responsible for the various tests for rheumatic activity such as the erythrocyte sedimentation rate revert to normal Under full treatment therefore the patient may appear to have recovered completely However upon withdrawal of therapy all the symptoms and abnormalities may rapidly reappear with an intensity as great as that which existed prior to the initiation of therapy

The current concept of the action of these drugs is that they interfere with the tissue reaction to the abnormal process but do little to accelerate its elimination from the body They serve the purpose therefore of reducing the inflammatory response and maintaining the patient in a state of relative well being while the body gradually disposes of the substances responsible for the disease

Salicylates may be given in the form of acetylsalicylic acid or sodium salicylate in a total daily dose of 0 064 gm (1 grain) per pound of body weight (0 15 gm per kg) varying from 3 gm in young children to 10 gm or more in adults given in equally divided doses at four hour intervals Individual variation in the efficiency of absorption or excretion of the drug and in its therapeutic effectiveness requires readjustment of the dose in many cases The aim is to give the minimum dose that results in full control of symptoms and to avoid serious toxic side reactions Studies on the concentration of salicylates in the blood have shown that it is usually necessary to attain a level of at least 25 mg per 100 ml to obtain full effect and that this concentration is sometimes reached with less than 0 064 mg per pound while at other times more is required

The most common toxic manifestations of salicylate therapy are nausea vomiting and gastric distress Tinnitus and some degree of temporary impairment of hearing usually occur at full therapeutic dosage Hyperpnea is commonly seen but the severe acidosis characteristic of intoxication with methyl salicylate rarely occurs in the course of treatment of rheumatic fever Occasionally mental disorientation and delirium may be seen as a manifestation of salicylate toxicity In practice nausea and vomiting are the most frequent causes of difficulty in maintaining an adequate dosage of the drug Although this toxic effect is not due solely to local action on the gastric mucosa it is sometimes beneficial to use enteric coated drug In addition better tolerance of the drug is established if the initial dosage is somewhat below the optimum and gradually increased over a period of a few days The use of sodium bicarbonate is contraindicated because it reduces the efficiency of absorption of salicylate

Hormonal Therapy Ideal dosage schedules for the use of the hormone products in rheumatic fever have not yet been determined The most generally accepted procedure at the present time is to begin with relatively large doses until the activity of the disease appears to be under control and then to reduce the dosage to the minimum amount which will maintain full effect The initial dose of *corticotropin* is 1 0 to 2 0 mg per pound per day given intramuscularly in four equal doses at six hour intervals The use of *cortisone* or *prednisone* offers the advantage of oral administration The initial dose of cortisone is 2 to 4 mg per pound per day in divided doses and that of prednisone one fourth this amount The full effect is usually obtained within one or two days and the dose can then be adjusted to the smallest amount that will suppress all symptoms and signs of the disease This serves to minimize the side effects associated with hyperadrenalism The possibility that continued administration of large doses may reduce the incidence of permanent heart damage is still under investigation

In two separate areas auxiliary therapy is required to counteract certain effects of the adrenal hormones unrelated to control of the rheumatic process Because of the effect of the hormones on the salt and water balance of the body a *low sodium* diet should be provided This is of particular importance in the presence of extensive carditis when accumulation of fluid may increase the risk of cardiac failure

tated patient and the newborn infant appear to be especially susceptible to infections Presumably staphylococcal infections arise from carriers and from environmental contamination but the relative importance of these two sources of organisms is unknown

Treatment Certain general principles should be followed in the treatment of all staphylococcal infections Of primary importance is the surgical drainage of abscesses since the available antistaphylococcal drugs are markedly reduced in effectiveness in the presence of pus Before the days of antimicrobial therapy patients with bacteremia were occasionally cured by the drainage of an abscess

In general the drugs useful in the treatment of staphylococcal infections include penicillin erythromycin novobiocin bacitracin the tetracyclines chloramphenicol and streptomycin Treatment must be prolonged since the organisms are killed slowly This is in striking contrast to the rapid bactericidal action of certain of these drugs notably penicillin on pneumococci or group A streptococci It is difficult if not impossible to recommend a single therapeutic regimen for all staphylococcal infections because the susceptibility of the various strains of staphylococci to each antimicrobial drug appears to be changing rapidly Indeed the drug of choice in certain geographical areas may be relatively ineffective in others Infections acquired in the general population are frequently susceptible to penicillin whereas staphylococcal disease contracted in the hospital may be resistant to therapy with penicillin or with the other antimicrobial drugs commonly employed in that clinic The nature and location of the infection also alter the method of treatment Sufficient data are not available to allow critical evaluation of the use of combinations of antimicrobial drugs in the treatment of staphylococcal infections

Drug susceptibility tests of the infecting strain of staphylococcus are invaluable in guidance of therapy In areas where such tests cannot be obtained penicillin streptomycin with penicillin or erythromycin should be administered in full dosage and if a favorable response is not observed after a few days therapy should be altered In severe infections initial therapy should include penicillin or erythromycin in combination with either streptomycin or bacitracin The latter drug should be given in doses of 15 000 to 20 000 units four times daily and should not be employed if there are signs of renal failure The choice of drug or combination of drugs after the first few days of treatment should be governed by the results of the drug susceptibility studies of the strain of staphylococcus involved

Within the hospital every effort should be made to prevent the spread of staphylococcal infections The patient exhibiting such an infection should be isolated for protection of personnel and other patients The indiscriminate use of antimicrobial drugs should be avoided since drug resistant strains are maintained in the hospital by such practices In the larger hospital it is advisable to withdraw one antimicrobial drug from general use so that when serious staphylococcal infections arise the drug may be used to combat them

Furuncles and Carbuncles

Definition A *furuncle* or boil is a circumscribed suppurative inflammatory lesion of the skin and the immediate subcutaneous tissues A *carbuncle* which may be considered a furuncle with multiple foci develops when a suppurative infection occurs in thick inelastic skin and extends into the deeper layers of fibrous tissue

Etiology Furuncles and carbuncles are most commonly caused by *Staphylococcus aureus*

Symptoms Although furuncles occur in any location they are especially prone to occur on the face neck forearms axillae midline and upper part of the back breasts groins and legs Carbuncles are essentially limited to the nape of the neck and back

Careful observation will show that most of these infections begin with a small pustule at the base of a hair follicle At this stage there is no pain perhaps only an itching sensation Within a few hours swelling and redness occur and some pain is experienced Gradually over a period of three to five days the boil becomes elevated the involved area is exquisitely tender and movement of the involved part causes pain At the apex of the swelling the skin glistens and becomes thinned and a yellow spot appears The boil is now said to be pointing and shortly will drain spontaneously The pus is creamy yellow in color and at the center of the boil a hard core may be evident

At the time of rupture of the abscess pain is relieved almost immediately The abscess continues to drain a serosanguin

Staphylococcal Infections

Introduction

Staphylococci are responsible for most suppurative infections of the skin and not infrequently cause infection of the lungs bones kidneys and other organs Typically such infections are associated with abscess formation

Staphylococci may be divided into three species according to the color of pigment produced Pigment production is best demonstrated in freshly isolated strains grown on solid medium at 22° C *Staphylococcus aureus* is golden yellow *S albus* is white and *S citreus* forms a lemon yellow pigment Strains of *S aureus* are responsible for the majority of infections in man *S albus* may occasionally cause mild infections *S citreus* rarely infects man

Staphylococcus aureus produces toxic substances with hemolytic necrotizing leukocytolytic and lethal properties A small number of staphylococci produce an enterotoxin which is responsible for most cases of food poisoning In addition they produce an enzyme hyaluronidase or spreading factor which hydrolyzes hyaluronic acid Although antiserums to some of these toxic substances have been prepared they have not proved especially useful in the treatment of infections in man

Pathogenic strains of staphylococci may be recognized by several methods Most *strains isolated from infections ferment* mannite Another characteristic of pathogenic strains is their ability to grow in human whole blood whereas nonpathogenic strains are easily killed in the bactericidal test The ability of certain staphylococci to coagulate plasma has long been recognized and used as a laboratory test for pathogenicity Recently the mechanism of th s reaction has been elucidated Staphylococcal coagulase reacts in some way with a factor (reacting factor) present in blood to produce a clotting substance Coagulase is antigenic and after infection an antibody develops which inhibits the coagulase reaction In order to demonstrate such antibodies the specific coagulase produced by the infecting strain must be utilized

Pathogenesis Invasion of the tissues by pathogenic staphylococci follows a rather characteristic course The organism multiplies locally and is probably facilitated in its spread by the production of hyaluronidase which increases the permeability of the connective tissues The organism may be protected from the phagocytic cells by the deposition of a thin barrier of fibrin at its periphery through the production of coagulase The organisms multiply locally and produce toxins and more coagulase Presumably coagulase diffuses into the surrounding tissues and accounts for local thrombosis in the blood vessels The toxins meanwhile cause marked inflammatory changes in the tissues and necrosis occurs centrally Eventually the abscess ruptures and repair of the tissue begins Occasionally when the organism is especially virulent the local barriers break down and bacteremia becomes evident Certain animals notably birds do not develop abscesses when pathogenic strains of staphylococci are injected This may be due to the fact that coagulase fails to act on plasma of birds because of an apparent deficiency in the amount of reacting factor in the blood

Epidemiology By means of bacteriophage typing the epidemiology of staphylococcal infections has been clarified to some extent It has long been recognized that staphylococci may be cultivated from various parts of the body More than half of the population carry *Staphylococcus aureus in the nasal* secretions and most persons harbor the same organism on the skin Nasal carriers *are especially likely to be skin carriers* The fact that the bacteriophage types of the organisms isolated from the nose and skin of one person are the same suggests a common source Apparently the skin is being continuously contaminated by the nasal secretions Staphylococci are most frequently found on the backs of the hands over the forearm and back of the neck and somewhat less commonly along the midline of the body and in the inguinal folds

In recent years it has become apparent that the hospital is a major source of serious staphylococcal infections In this environment where many patients are receiving *various antimicrobial drugs* strains of staphylococci resistant to these drugs are constantly present These strains are likely to be especially virulent They may be isolated from patients and staff as well as from dust blankets clothing and air Furthermore the postoperative or debili

plication of staphylococcal bacteremia Staphylococcal pneumonia also develops in patients receiving antimicrobial drugs for other infections *Fibrocystic disease of the pancreas* is often complicated by chronic staphylococcal infections of the lung

Morbid Anatomy The mucosa of the trachea and bronchi is ulcerated and intensely inflamed and is covered with thick purulent secretions Around the bronchi the alveoli are filled with an inflammatory exudate containing blood and fibrin Multiple small abscess pockets are observed some communicating with bronchi Necrosis of the lung parenchyma is prominent

Symptoms Staphylococcal pneumonia is usually preceded by a respiratory infection the symptoms of which may include sore throat cough or generalized malaise and fever After a variable period of one to several days the patient suddenly becomes quite ill The temperature increases there may be a rigor and the cough becomes aggravated and productive of purulent sputum At times the sputum may be streaked with blood or is brownish or yellowish in color Pleuritic pain is common

In some patients the course of the disease may be rapidly fatal with a sudden onset prostration a peculiar reddish blue cyanosis rapid respirations and high fever In others the disease appears to be more chronic with remittent fever but moderately rapid pulse

The physical signs in patients with staphylococcal pneumonia are not characteristic but are variable Early there may be no change in the percussion note later dullness to percussion is exhibited Rales both coarse and fine may be elicited over the involved area of the lung Since pleural effusion and empyema are common dullness and other signs of fluid may be found

The leukocyte count is elevated to between 15 000 and 25 000 per cu mm rarely it is low or normal Roentgenograms of the chest show one or more areas of consolidation near the hilum of the lung Later cavities may develop and their fluid levels can be easily demonstrated in the roentgenogram Pleural fluid is common

Diagnosis Cyanosis remittent fever and purulent sputum should lead one to suspect staphylococcal pneumonia The diagnosis is dependent on the isolation of *S aureus* in relatively pure culture from the sputum The development of empyema from the fluid of which staphylococci may be cultured aids in the establishment of the diagnosis Abscess formation as shown by the roentgenogram is characteristic The blood culture which should be made in each case is usually sterile When bacteremia is present the pneumonia may be secondary to a focus elsewhere in the body

Differential Diagnosis One must consider all other forms of bacterial pneumonia and primary atypical pneumonia in the differential diagnosis Abscess formation is most apt to occur in staphylococcal streptococcal and klebsiella (Friedlander s bacillus) pneumonia Pneumonia caused by the Friedlander bacillus is confused with staphylococcal pneumonia because of the remittent character of the temperature Careful culture of the sputum is the only method of establishing the diagnosis

Prognosis Most patients recover from staphylococcal pneumonia but a few succumb The illness in those who recover usually lasts three or four weeks and recovery is gradual

Treatment As in all severe infections the staphylococcus isolated from the patient should be tested for susceptibility to the various antimicrobial drugs If the organism is susceptible to penicillin 2 000 000 to 4 000 000 units should be administered in divided doses every four hours It is also advisable to administer streptomycin Bacitracin or erythromycin may be substituted for streptomycin if the organism is susceptible to one or another of these drugs Treatment should be maintained for at least one week after the temperature returns to normal As in other staphylococcal infections the temperature falls slowly after institution of specific therapy Empyema should be treated early by the intrapleural injection of 50 000 to 100 000 units of penicillin every twenty four to forty eight hours The intrapleural installation of the enzymes streptokinase and streptodornase is advisable as discussed in a later section on Empyema If the intrapleural fluid is thick surgical drainage may be required in addition to penicillin therapy

The general management of the patient with staphylococcal pneumonia is identical with that described in the section on Pneumococcal Pneumonia (p 126)

Osteomyelitis

Definition Osteomyelitis is an infection of the bone most frequently caused by *Staphylococcus aureus*

Etiology Staphylococci reach the bone after invasion of the blood stream The

eous fluid swelling decreases and within a few hours to days the discharge ceases Redness may persist for several days or weeks but eventually all signs of the ab scess disappear

Although this description applies to the majority of boils certain features of these infections deserve emphasis Infections of the hair follicles which never involve the surrounding tissues are known as simple *folliculitis* They are apt to occur in persons who are in constant contact with oil grease and other skin irritants People with promi nent sebaceous glands are prone to suffer staphylococcal infection which the derma tologists designate as *pustular acne vul garis* These infections are seen over the face and the upper part of the back

Furuncles occasionally occur in the axilla but most infections in this region arise in the sweat glands hence the name *hidradenitis* These infections start as small inflammatory nodules which cause consid erable discomfort When the abscess dis charges the organisms invade other sweat glands and hair follicles with subsequent scarring of the tissues

A single boil may be followed by multiple infections of the surrounding skin *i e furunculosis* The secondary infections are due to the purulent discharge from the abscess invading other hair follicles in the adjacent skin Boils around the nose and lips are especially dangerous since local trauma may result in the invasion of the venous sinuses within the skull

Characteristically the *carbuncle* occurs at the nape of the neck and begins with infection of one or usually several hair follicles As a result the area of swelling and redness is wide and the surface is covered with multiple pustules As the infec tion spreads the center becomes a grayish yellow crater with ragged edges Most car buncles are extremely painful although occasionally they cause little discomfort The patient s head is usually held rigidly Older persons may be critically ill and bacteremia is common

Diagnosis Simple *folliculitis* is frequently caused by *Staphylococcus albus* and is easily recognized because of the lack of redness and induration around the hair fol licle *Pustular acne vulgaris* is always asso ciated with an oily skin Most furuncles are not associated with a constitutional reac tion whereas a person with a carbuncle frequently has fever and leukocytosis Cul tures of the boil or carbuncle show coagu lase positive *S aureus* Since diabetics are subject to carbuncles and boils the urine should be examined for sugar in all patients with these infections

Treatment When a furuncle or carbuncle is observed before there are signs of abscess formation the daily intramuscular injec tion of 600 000 units of procaine penicillin and/or the administration of 0 5 gm of erythromycin every six hours may abort the process Usually treatment must be given for at least one week In the presence of fever a blood culture should be obtained and the dose of penicillin increased The application of hot packs to the infected area may relieve pain and aid in the localization of the infection In all severe infections the involved part should be immobilized and the patient kept in bed

In well localized abscesses the cavity should be drained and antimicrobial ther apy continued until signs of inflammation have disappeared Moist dressings should not be applied to the skin after the abscess drains since moisture tends to macerate the skin and facilitates the implantation of organisms The skin around draining sinuses should be protected by a thick layer of penicillin or tyrothricin cream

Prevention The prevention of furuncles or carbuncles is difficult probably because the skin is being continuously contaminated via the hands with virulent staphylococci from the nasal secretions The patient should be cautioned not to traumatize the skin and to avoid oils dirt and other skin irritants and to use mild soaps and cool water when washing Such procedures de crease the opportunity for invasion of hair follicles and sebaceous or sweat glands When infections recur frequently the daily application of tyrothricin cream is recom mended Such advice is especially indi cated in diabetic patients since recurrent boils are common

Staphylococcal Pneumonia

Definition Pneumonia caused by *Staphy lococcus aureus* is characterized by abscess formation

Etiology Staphylococcal pneumonia is relatively rare except during periods when there are epidemics of influenza measles or whooping cough The exact cause for this relationship is unknown Both in the primary form and in pneumonia secondary to other respiratory infections staphylo cocci probably invade the parenchyma of the lung through the bronchial and bron chiolar walls Isolated areas of pneumonia with abscess formation are a common com

and this drug should be given in relatively large amounts Usually 200 000 to 2 000 000 units are injected intramuscularly every three to four hours In addition either 0 5 gm of streptomycin or 0 5 gm of erythromycin every six hours is advisable Every effort should be made to isolate the infecting organism so that therapy may be altered according to the results of drug sus ceptibility tests Treatment is continued for a minimum period of three weeks During the later period of therapy procaine penicillin may be substituted for the sodium salt in dosages of 600 000 units twice daily Such therapy instituted within four days of onset usually results in the subsidence of signs of inflammation within two to four days and minimal or no damage to the bone can be demonstrated in the roentgenogram In those patients whose disease has been present for four days or longer local ized abscesses may form and damage to the bone is more extensive Small sequestra usually absorb but larger pieces of dead bone may require removal In addition to these measures the fluid balance is to be maintained and severe degrees of anemia should be corrected by blood transfusion

Chronic Osteomyelitis The treatment of chronic osteomyelitis usually requires se questrectomy saucerization of the infected bone and removal of the sinus tract The antimicrobial drugs in the amounts al ready indicated should be administered before and after operation In a few pa tients intensive penicillin treatment alone results in eradication of the disease

Staphylococcal Bacteremia

Pathogenesis Staphylococci may invade the blood stream from abscesses in any location The studies of Skinner and Keefer have demonstrated that infections of the skin account for the primary focus in about 40 per cent of the cases Infections of the bone and respiratory tract account for an other 40 per cent and in the remainder the bacteria are fed into the blood stream from the genitourinary tract or from an unknown focus

Factors which contribute to the fre quency of blood stream invasion are trauma and the presence of debilitating disease Early incision of an abscess or attempts to evacuate the pus by squeezing may result in bacteremia Such procedures are espe cially dangerous when the boil is located about the face Bacteremia occurs fre quently in patients with diabetes arteriolo sclerosis cancer and other debilitating dis eases Operations especially prostatic resections are likely to be the source of the bacteremia Virulent staphylococci are more likely to produce a fatal bacteremia than nonvirulent organisms belonging to the coagulase negative group Fortunately bacteremia following infections of the skin is rare In 11 568 patients seen with car buncles and furuncles Sutherland observed only 7 instances of bacteremia

Symptoms Typically the patient has chills and fever after invasion of the blood from a boil or carbuncle The fever may be high and remittent in type or less fre quently intermittent In a few cases the fever is low and continuous Rigor is ob served in about 25 per cent of patients Marked perspiration is common Com plaints such as headache and malaise are frequent but not characteristic of the disease

One of the characteristic features of *Staphylococcus aureus* bacteremia is the production of metastatic abscesses whereas *S albus* does not produce such lesions Patients who survive *S aureus* bacteremia more than a few days get abscesses The most frequent sites of these metastatic ab scesses are the skin subcutaneous tissues and the lungs

Infection of the lung is a common com plication of staphylococcal bacteremia For this reason every effort should be made to locate the portal of entry of the staphylo coccus in patients with pneumonia and a positive blood culture It will be recalled that primary staphylococcal pneumonia is not commonly associated with bacteremia

Superficial abscesses of the skin joints and muscles account for 30 per cent of the metastatic complications Petechiae and purpura are occasionally seen Internal ab scesses of the kidneys brain and spinal cord are not uncommon

Infection of the pleural peritoneal and pericardial cavities occurs in less than 10 per cent of cases Sinus thrombosis and meningitis are rare and usually occur as the result of direct extension of the infec tion Endocarditis should be suspected when there are cardiac murmurs which change in character or whenever bacteremia per sists in the absence of an obvious extra cardiac focus

Diagnosis and Prognosis The history of a preceding staphylococcal infection in a patient with intermittent fever should sug gest the diagnosis of staphylococcal bac

usual focus is a wound furuncle or other external infection The initial acute infection is practically confined to children and is more frequent in boys than in girls The usual explanation for localization in the bone is the fact that the diaphysis of the child gets its blood supply through terminal capillary loops The bacteria tend to settle out in this area The fact that the blood of the young child contains little coagulase reacting factor as compared with that of the adult may possibly account for the initial blood stream invasion in the younger age groups

Pathogenesis and Morbid Anatomy The staphylococci set up an acute inflammatory reaction with necrosis of the bone The initial infection occurs at the diaphysis and seldom crosses the epiphysis instead as the infection progresses the pus emerges to the surface of the bone raising the periosteum Although purulent material is present at an early stage the bone is not destroyed immediately As the bone dies *sequestra* are formed Repair begins after drainage of the abscess small sequestra may be absorbed and new bone is laid down by the osteoblasts forming the *involucrum* Not infrequently a chronic infection of the bone is established which intermittently results in an acute inflammatory process

Symptoms Acute osteomyelitis is usually ushered in by fever chills pain and in the very young patient by nausea and vomiting Careful examination may reveal a recently healed wound pustule or furuncle Pain over the bone may be the only early sign of localization of the infection Tapping on the bone may cause pain referred to the involved area Pain sometimes skips around to various bones before it finally localizes Muscle spasm around the involved bone is a common and frequently early sign of osteomyelitis At this stage of the disease roentgenograms of the bone reveal no abnormality

As the infection progresses redness and swelling occur over the involved bone The patient splints the limb or affected part for movement causes pain When the infection is near a joint swelling of the periarticular tissues occurs and effusion into the joint is common The temperature is likely to be high and the patient critically ill By ten days to two weeks after the onset the roentgenogram may show some rarefaction of the bone Subsequently periosteal reaction is exhibited by new bone formation As the bone dies dead bone or sequestrum may be observed in the roentgenogram

Chronic osteomyelitis is especially likely to occur if sequestra remain unabsorbed or if adequate drainage is not established Repeated attacks of acute osteomyelitis with the establishment of chronic draining sinuses characterize this phase of the disease Amyloidosis is a complication of the prolonged suppurative process

Diagnosis During the first few days of the disease the history of fever chills and pain over long bones is enough to suggest the diagnosis of acute osteomyelitis There is usually a leukocytosis of 20 000 or more cells per cu mm and the blood culture frequently shows *Staphylococcus aureus* As the disease progresses anemia develops After ten days the roentgenogram exhibits diagnostic abnormalities such as periosteal new bone formation and sequestra

Acute osteomyelitis must be differentiated from other bacterial infections and erythema nodosum Usually the diagnosis is not difficult A serious error can be made however if a patient with acute osteomyelitis is mistakenly considered to be suffering from *acute rheumatic fever* A history of recent furunculosis with or without trauma the usual monoarticular involvement the degree of leukocytosis (20 000 or more cells per cu mm) the response to penicillin and in some cases the demonstration of staphylococcemia all serve to establish the presence of acute osteomyelitis This question of the differences between rheumatic fever and osteomyelitis is also discussed in the section on Rheumatic Fever (p 155)

Treatment and Prognosis Before the introduction of penicillin the case fatality rate for patients with acute osteomyelitis was about 15 per cent in the absence of bacteremia and 25 to 50 per cent in the presence of bacteremia If the patients survived the initial infection a chronic infection was usually established and metastatic foci in other bones were common Today death from acute osteomyelitis is rare and chronic osteomyelitis is uncommon

Acute Osteomyelitis In order to avoid surgical intervention early treatment of acute osteomyelitis is required For this reason it is advisable not to wait for bacteriological or roentgenographic confirmation of the diagnosis before starting antimicrobial therapy The initial attack of osteomyelitis is usually caused by an organism susceptible to the action of penicillin

enhanced by incubating the cultures in an atmosphere containing 2 to 10 per cent carbon dioxide

Colonies of *N gonorrhoeae* are gray and translucent and their recognition is aided by performing the oxidase test A 1 per cent solution of p aminodimethylaniline monohydrochloride is poured over the surface of the agar plate and within a few minutes colonies of the gonococcus turn pink then purple A positive test occurs with all members of the genus *Neisseria* and occasionally with certain other bacteria With cultures from the genital tract a positive oxidase reaction together with characteristic colonial morphology and the presence of gram negative diplococci constitutes presumptive evidence that the organism is a gonococcus However since saprophytic *Neisseria* and other bacteria are known to produce false positive results particularly in women confirmatory fermentation reactions with glucose maltose and sucrose should always be performed Carbohydrate reactions are also used to differentiate gonococci from meningococci when positive cultures are obtained from blood cerebrospinal or joint fluid Meningococci ferment both dextrose and maltose while the gonococcus gives a positive reaction only with dextrose Differentiation can also be accomplished by agglutination tests

Since the gonococcus is quickly killed by drying exudates from the genital tract should be cultured directly on agar plates or the swab should be placed in a small amount of broth while it is transported to the laboratory Urine should be centrifuged and the sediment inoculated on the culture plate With cerebrospinal fluid blood and synovial fluid in which the number of organisms may be small and contaminating bacteria are usually not present the best results are often obtained by culturing the specimens in shallow layers of broth enriched with plasma or ascitic fluid using an increased tension of carbon dioxide

Epidemiology and Pathogenesis Gonorrhea is world wide in distribution and all races appear to be equally susceptible There is considerable individual variation in resistance to infection however the nature of which is not known Even when massive numbers of gonococci are instilled directly into the urethral canal less than half the males so inoculated contract the disease

Accurate information concerning the incidence of gonorrhea is difficult to obtain since reporting is poor and penicillin is so easily obtainable that many cases are treated by persons other than physicians The evidence available indicates that there probably has been a marked decline in the total number of infections since 1945 The disease is still widespread however and is prevalent chiefly among lower income groups Moreover the lack of immunity following a gonococcal infection makes it possible for a person to have a number of attacks Analysis of such "repeaters indicates that in most instances they are either indifferent or are unable to comprehend the facts of prevention and treatment Transmission of gonorrhea by asymptomatic carriers also tends to propagate the disease This problem is aggravated by the difficulty in detecting and in eradicating the carrier state especially in women

The resistance of stratified squamous epithelium to infection by the gonococcus explains the lack of lesions on the external genitalia of both sexes and in the vagina The susceptibility of columnar epithelium permits infection of the urethra prostate seminal vesicles epididymis and glands associated with these structures in the male In women infection occurs chiefly in the urethra Skene s and Bartholin s glands endocervix and fallopian tubes Once established the infection tends to persist for weeks or months in the genital tract unless treatment is given This tendency toward chronicity was one of the factors chiefly responsible for the spread of the disease before effective chemotherapy became available Persistence of the infection is associated with tissue destruction and abscess formation leading to urethral strictures in the male and chronic inflammation and sterility in the female In a small percentage of cases the organisms find their way into the blood stream and set up metastatic foci in distant organs such as the joints and endocardium

Nonvenereal transmission of infection by the gonococcus occurs rarely if at all Instillation of penicillin or silver compounds into the eyes of newborn babies has virtually eliminated ophthalmia neonatorum formerly an important cause of blindness Epidemics of vulvovaginitis in young girls were once though to be neisserian in nature and to be transmitted by bedclothes and towels It is now realized however that in most instances the gonococcus is not the causative agent and when it is sexual contact has occurred

Symptoms and Signs From two days to two weeks following sexual exposure burning on urination is the first symptom of gonorrhea usually noted in the *male* and

teremia The finding of multiple peripheral abscesses also suggests such a diagnosis Most patients exhibit a high leukocyte count and anemia The diagnosis is established by the isolation of the organism from the blood stream

Before the introduction of modern chemotherapy the case fatality rate was 80 per cent

Treatment The therapy of staphylococcal bacteremia is still unsatisfactory Every effort should be made to drain all abscesses promptly and treatment should be guided by drug susceptibility tests In general combinations of drugs are usually employed The compounds most frequently used are penicillin erythromycin and streptomycin The tetracycline drugs chloramphenicol novobiocin and bacitracin are given if the organism is susceptible to their action Each drug should be given in the maximum dose that can be tolerated Blood transfusions should be given to patients with anemia

Enterocolitis

For many years the surgeon has recognized a serious postoperative complication enterocolitis which is characterized by the sudden development of diarrhea vomiting abdominal distention tachycardia fever hypotension and shock More recently a similar syndrome has been observed in other hospitalized patients especially those receiving wide spectrum antimicrobial drugs Most cases are apparently caused by staphylococci since these organisms may be recovered in large numbers from the feces Characteristically the staphylococci isolated from the stool produce enterotoxin and are resistant to the antimicrobial drug or drugs being administered to the patient For further discussion of this subject see Enterocolitis (p 839)

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Gonococcal Infections

Definition *Gonorrhea commonest of the* venereal diseases is the principal infection caused by the gonococcus (*Neisseria gonorrhoeae*) From the primary focus in the genital tract the organism may spread to involve other parts of the body particularly synovial tissues and serosal surfaces causing a variety of clinical entities such as arthritis endocarditis and meningitis Formerly common and important extragenital infections with the gonococcus have become rare since the advent of penicillin

Etiology and Bacteriology As seen in smears of purulent exudates the gonococcus is a gram negative kidney shaped diplococcus often located within the cytoplasm of polymorphonuclear leukocytes This characteristic appearance was first observed in urethral pus by Neisser in 1897 In cultures single cells tend to predominate and the flattening of one surface of the oval is often absent

Primary cultivation of the gonococcus is difficult because of its fastidious growth requirements and its susceptibility to toxic substances often present in culture media Blood is commonly used for enrichment and the deleterious effects of certain amino acids are reduced by heating the medium after the blood is added (chocolate agar) Toxic materials present in agar can be neutralized by the addition of starch or charcoal Dyes such as Nile blue inhibit the growth of contaminating bacteria but do not affect the growth of the gonococcus Media are commercially available which take advantage of all the known facts concerning growth requirements so that routine cultural techniques are now quite simple The results still leave much to be desired however since the reproducibility in different laboratories using the same cultural techniques is not greater than 75 per cent The growth of most strains is

involved Finally there is a group of patients in whom the onset and clinical course are indistinguishable from that of rheumatoid arthritis The gonococcal infection may provide a "trigger mechanism for the initiation of this disease However some investigators on careful questioning have elicited histories of previous attacks and believe that the gonococcal infection is usually an incidental occurrence in rheumatoid subjects

Differentiation of gonococcal arthritis from rheumatoid arthritis and acute rheumatic fever is in many instances very difficult A clear-cut history of gonorrhea may be unobtainable and it is often impossible to culture gonococci either from the genital tract or the joint fluid The gonococcal *complement fixation test* is helpful in some cases particularly when it is negative initially and then shows a rising antibody titer after several weeks This test which requires carefully prepared and standardized reagents is not performed in the ordinary laboratory but is available through most state laboratories

Reiter s disease characterized by urethritis arthritis and conjunctivitis also offers serious diagnostic difficulties especially since a catarrhal form of conjunctivitis occurs in 10 per cent of patients with gonococcal arthritis

Penicillin reactions and *gout* are other disorders which can cause confusion Since a precise diagnosis is often impossible during the early stages therapy must be started empirically and the response to salicylates or to penicillin is often helpful in establishing the true cause

Other complications such as meningitis myelitis liver abscesses and keratodermia blennorrhagica are now so rare that they have become medical curiosities

Diagnosis Gonococcal urethritis is readily diagnosed in both sexes when the typical clinical picture is present and gram negative intracellular diplococci are seen on smears of the urethral discharge Symptoms are sometimes mild and transient in the male however and endocervicitis may pass unnoticed in the female Unfortunately there is no reliable method available especially in females for detecting the carrier state Negative cultures do not provide adequate evidence that a person is unable to transmit the disease Aside from genital infections the main problems in diagnosis occur with arthritis and salpingitis the salient differential features have been covered in the preceding section

Treatment and Prognosis Penicillin is the drug of choice for the treatment of gonococcal infections In gonococcal *urethritis* a single intramuscular injection of 600 000 units of procaine penicillin will cure over 95 per cent of cases in both males and females This dose is also adequate to abort syphilis Longer acting forms of penicillin either the aluminum monostearate form of procaine penicillin or the newer benzathine penicillin G may also be used Recent studies indicate that a single dose of 1 200 000 units of benzathine penicillin G which gives measurable drug concentrations in the blood for three to four weeks is effective particularly in women both in eradication of the carrier state and in prevention of reinfections Cultures should be performed at weekly intervals for three or four weeks if these are negative the patient can be considered cured It is common especially in males to have a slight mucoid urethral discharge for weeks or months even when the cultures are negative This is regarded by some authorities as a nonspecific form of urethritis which is acquired at the same time as the gonococcal infection and it is said to respond to therapy with oxytetracycline Until this view is better substantiated it is probably best to regard the persistent discharge as a manifestation of subsiding inflammation which usually disappears spontaneously and requires no therapy Retreatment is indicated in the small number of patients whose cultures remain positive Treatment failures are not due to the development of penicillin resistant gonococci and few if any cases fail to respond to a second course of therapy consisting of two to four daily injections To be certain that the therapy has been effective in preventing syphilis serological tests should be performed for four months

If the prostate seminal vesicles or epididymis is involved the patient should be put to bed and should receive 600 000 units of procaine penicillin two or three times daily for one or two weeks When abscesses form in the prostate or epididymis or there is a failure to respond to penicillin after two or three weeks surgery may be indicated

The same general principles are applicable in the management of acute *salpingitis* There is usually a prompt response to penicillin with subsidence of pain and a return of the temperature to normal within forty-eight hours Except for the drainage of abscesses surgery is not indicated in the acute stage Resection of infected tissues including all pelvic organs is per

is followed by the appearance of a purulent urethral discharge The infection tends to spread posteriorly and involvement of the posterior urethra is indicated by cloudiness in the second glass of voided urine Urinary retention may occur if the prostate is involved and infection of the seminal vesicles usually causes fever and pain which may radiate to various parts of the pelvis Acute epididymitis is associated with severe pain and tenderness and the testicle may become swollen Involvement of the epididymis is a serious complication which often leads to sterility Following treatment the signs and symptoms gradually subside but a slight mucoid discharge may persist for several weeks

In the *female* painful urination and vaginal discharge are the commonest early symptoms Involvement of Skene s or Bartholin s glands is usually indicated by reddening at the orifices but may lead to the formation of large painful abscess The notion that most Bartholin gland abscesses are gonococcal in origin has been disproved in most instances they are caused by other organisms such as streptococci Lower abdominal pain characteristically appears when the infection spreads from the cervix into the fallopian tubes The symptoms of acute salpingitis often appear quite abruptly and must be differentiated from those of appendicitis pyelonephritis and ectopic pregnancy Acute pelvic inflammatory disease is readily diagnosed when there is a history of recent sexual exposure tender adnexal masses are present bilaterally and gonococci can be demonstrated on cervical smears These aids are often not present however and differentiation of this condition from other causes of lower abdominal pain may be very difficult Surgical exploration is sometimes necessary to exclude conditions which require surgical management Salpingitis tends to recur causing fibrosis and destruction of the pelvic structures Abscesses form and pain and fever are present intermittently The patient is usually sterile and surgical removal of all the pelvic organs may eventually be necessary

Complications The establishment of metastatic foci secondary to invasion of the blood stream by gonococci is relatively uncommon at the present time Awareness that it can occur is important however since prompt recognition and adequate therapy often lead to complete recovery Transient bacteremia may occur without causing symptoms or there may be a shaking chill followed by a silent period prior to the appearance of symptoms caused by metastatic lesions Occasionally gonococci may invade the blood stream repeatedly over a period of weeks or months causing fever chills arthralgia and a variable skin rash This syndrome of *gonococcemia* is difficult to differentiate clinically from the commoner entity of *meningococcemia* Rarely *endocarditis* occurs and runs the malignant course characteristic of acute rather than subacute bacterial endocarditis In most cases there is no pre existing valvular damage The aortic valves are the commonest sites of involvement but next in order of frequency are the valves of the right side of the heart It is often difficult to obtain positive blood cultures and too few proved cases have been reported in the past decade to assess accurately the results of penicillin therapy

Arthritis is the commonest extragenital complication of gonorrhea Formerly a common and crippling disease this condition is now so rare that only a few cases are seen each year even in the larger city hospitals Arthritis occurred in 3 to 5 per cent of patients with gonorrhea in the pre penicillin days but the incidence is now probably not greater than one tenth of one per cent The onset is usually sudden consisting of an acute migratory polyarthritis which occurs from one to four weeks following the initial infection The knees wrists and ankles are most commonly affected but any of the joints in the arms and legs may be involved Rarely the infection may be limited to one of the less commonly involved joints such as the sternoclavicular or temporomandibular Tenosynovitis occurs more frequently than in any other type of arthritis and is present usually about the wrists hands and feet

The course of gonococcal arthritis is extremely variable Thin serous fluid may accumulate in several joints and in these cases it is often difficult to demonstrate bacteria in the joint fluid There is usually a prompt response to penicillin therapy however and complete recovery occurs within a few weeks In other instances the arthritis becomes monarticular after several days and the joint fluid is then more likely to be purulent and to contain gonococci which are demonstrable sometimes on smear but more often by culture Prognosis in this type of case is likely to be poor particularly when treatment is delayed Return of function to normal is unusual and limitation of motion which may progress to bony ankylosis is common especially when the wrist and hand joints are

Identification of meningococci is based on morphology fermentation of glucose and maltose and immunological reactions Four immunological types have been differentiated in the past by agglutination with specific antiserums but cross reactions are frequent particularly between types I and III For practical purposes therefore it seems advisable to consider only two immunological groups of meningococci group I to include the old types I and III and *group II* to include the remaining types and atypical strains Group I strains are encapsulated and many readily be identified immunologically by capsular swelling with homologous type specific antiserum One strain in group II termed group IIα is likewise encapsulated and thus may be similarly identified Other serological methods of identification such as precipitation and complement fixation may be used but are generally less simple and satisfactory than agglutination and capsular swelling

Substances termed "endotoxins may be extracted from living or dead meningococci Although the toxicity of such extracts for animals has been demonstrated there is little evidence of type or group specificity The production of a true type specific toxin or "exotoxin by the meningococcus has been reported but most authorities question its existence

Epidemiology Sporadic meningococcal infections occur almost constantly throughout the world Epidemics tend to recur irregularly in five to ten year cycles superimposed on an annual seasonal increase the peak month of which is usually March in temperate zones In the United States and Canada the reported incidence of meningitis has been slowly falling annually since 1953 The susceptibility of the general population is low and morbidity rates for clinically apparent disease are seldom higher than 10 to 1000 per 100 000 in the exposed population during epidemic periods Infants and children are most frequently attacked in one series of 3557 cases 27 per cent of the patients were less than five years of age and 45 per cent were less than fifteen The incidence is usually higher in males than in females Race and color have no known influence on incidence or susceptibility The higher rates reported among Negroes in certain urban areas have been attributed primarily to crowding The exact incubation period is unknown but probably is between one and ten days

The portal of entry of the organisms is the upper respiratory passages and transmission from person to person presumably may occur by direct or intimate contact by airborne droplets or by articles contaminated with secretions of the respiratory tract Even during severe epidemics however the majority of clinical infections have no apparent connection with one another and case to case spread is usually impossible to trace Cultural surveys during periods of high incidence have shown that more than 90 per cent of the population harbor meningococci in the nasopharynx either constantly or intermittently during an outbreak without clinical evidence of infection (carriers) During interepidemic periods the organism may be recovered from less than 5 per cent of persons examined Even under conditions of low carrier prevalence however a considerable proportion of the population will harbor meningococci at some time during a period of weeks or months since the respiratory tract flora is not static but changes constantly through acquisition of new bacteria and their subsequent loss

Morbid Anatomy In carriers or *inapparent infections* abnormal reactions are ordinarily not found *Meningococcemia* is characterized by focal hemorrhages into cutaneous subcutaneous submucosal and synovial tissues The fundamental lesion is vascular in character with endothelial damage inflammation of the vessel wall necrosis and thrombosis The classic finding in rapidly *fulminating meningococcemia* the *Waterhouse Friderichsen syndrome* is bilateral adrenal hemorrhage Damage to the adrenal cortex may occur without hemorrhage (Banks)

Involvement of the central nervous system is characterized by *meningitis* which progresses from hyperemia and an increased amount of cerebrospinal fluid to a purulent exudate organizing if the disease becomes chronic

Pathological Physiology and Chemistry The present theory of the pathogenesis of meningococcal infections is that the bacteria enter the body through the upper respiratory passages and become implanted in the membranes of the nasopharynx and adjoining structures Symptoms and signs of acute upper respiratory infection may then result Direct invasion of the blood stream takes place from these sites and evidences of bacteremia appear Dissemination of the meningococci is followed by metastatic lesions in various sites such as skin meninges joints eyes ears and lungs The symptoms and signs are dependent on the site of localization In meningitis two

formed in chronic cases only when there is failure to respond to conservative management over a period of eight to twelve months

Penicillin either crystalline or procaine is often administered in doses much larger than those specified In the opinion of the writer this is rarely necessary For patients who cannot be treated with penicillin because of sensitivity reactions tetracycline or one of its derivatives is effective Two grams (0 5 gm every six hours by mouth) are adequate for uncomplicated gonorrhea and the same dosage may be continued for one or two weeks when complications are present

Gonococcal *arthritis* usually responds well to rest and penicillin if treatment is started early before the joint fluid becomes thick and purulent and tissue destruction has occurred Because of the diffusibility of penicillin it is not necessary to inject the drug into the joint cavity The involved joints should be kept in good position but prolonged immobilization is rarely indicated The temperature usually remains elevated for seven to ten days but pain may persist for several weeks Penicillin should be administered for about two weeks in most cases Occasionally thick pus persists despite intensive therapy and surgical drainage may be necessary Physical therapy is a valuable adjunct in promoting return of function in the convalescent stage Failure to respond to penicillin is often helpful from a diagnostic standpoint for as has been pointed out the differentiation of gonococcal arthritis from other forms of acute arthritis is often difficult Large doses of crystalline penicillin G (5 000 000 to 10 000 000 units daily) should be used in the treatment of gonococcal *endocarditis* and *meningitis*

Prevention Gonorrhea can be prevented by ingesting a single penicillin tablet (250 000 units) within three or four hours after exposure Unfortunately this simple remedy has not been widey used so far by those who need it most Programs of case finding and education leave much to be desired Prompt treatment of contacts of males with acute gonococcal urethritis the so called "speed zone technique" has been quite successful in some cities

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Meningococcal Infections

Definition Meningococcal infections are manifestations of a specific infectious disease characterized by infection of the upper respiratory tract invasion of the blood stream (meningococcemia) and focal involvement of various sites notably the central nervous system (meningococcal meningitis cerebrospinal fever spotted fever or epidemic cerebrospinal meningitis) One or all of these features may be exhibited in a single patient Meningitis has occurred sporadically and epidemically since its first recognition in Geneva in 1805 by Vieusseux and in the United States by Danielson and Mann in 1806

Etiology The meningococcus (*Neisseria intracellularis Diplococcus intracellularis meningitis*) was established as the causative agent by Weichselbaum in 1887 It is a gram negative coccus variable in size and occurring singly or as biscuit shaped diplococci Certain strains are encapsulated The organism is fastidious in its metabolic requirements and will grow only on enriched laboratory media at body temperature Meat infusion broth or agar containing 5 to 10 per cent of blood (rabbit sheep or horse) or human ascitic fluid is an adequate medium Chocolate agar prepared by heating fresh blood agar is especially suitable for initial isolation Growth is augmented by incubating the cultures in an atmosphere containing 5 to 10 per cent of carbon dioxide Meningococci are easily killed by chilling or drying so that prompt inoculation and incubation of all cultures is desirable Because of the extreme susceptibility of meningococci to the sulfonamides para aminobenzoic acid in concentration of 5 mg per 100 ml should be added to media used for the culture of specimens from patients

Early in the disease there may be a generalized mottled erythema which appears dusky if the patient is slightly cyanotic Yellowish pink macules simulating the "rose spots" of typhoid wheals or nodules resembling erythema nodosum may appear before petechiae and ecchymoses Careful search in strong daylight may be necessary to detect the early lesions Occasionally vesicular pustular or bullous lesions are present superficial or deep ulcerations may result A common site for the lesions *first to appear is about the wrists and* ankles but any area of the body may be involved including the conjunctivas and the mucous membranes The hemorrhagic lesions fade to a brown rusty color three or four days after their appearance new crops may appear often following chills so that the rash may present a varied appearance

Other physical findings with the exception of splenomegaly are inconstant *Herpes labialis* is found in about 10 per cent of the cases Unless meningismus develops symptoms referable to involvement of the central nervous system are absent The symptoms of metastatic localizations are usually self-evident depending on the site involved

Laboratory examinations serve to establish the final diagnosis *Leukocytosis* varying from 12 000 to 40 000 cells per cu mm is almost constantly present From 80 to 90 per cent of the cells are neutrophils Occasionally intracellular diplococci may be seen *within the cells on a stained smear* of capillary blood or of blood obtained directly from a skin lesion Cultivation of meningococci from the blood furnishes final etiological proof It should be emphasized that repeated cultures of the blood may be necessary to detect the meningococcus and that growth of the organism in liquid culture medium may be delayed Other laboratory examinations give normal findings or results compatible with any febrile illness

The subsequent course is dependent on therapy although approximately 20 per cent of the patients recover spontaneously after several weeks or months Any of the complications and sequelae of meningococcal infections may develop

Acute fulminating meningococcemia differs from the milder form chiefly in the rapidity of its progress and its overwhelming character The onset is often abrupt and represents a dramatic departure from normal health with a shaking chill severe headache dizziness or vertigo collapse or unconsciousness Three forms may be differentiated (Banks) (1) The *adrenal* form is characterized by massive purpura low blood pressure clear mental condition rapid quiet respiration and overwhelming bacteremia The extensive rash (Fig 24) involves skin and mucous membranes as well as internal organs classically the adrenals The temperature may be subnormal normal or slightly elevated Within a few hours circulatory collapse develops Adrenal hormone replacement therapy may help to sustain these patients (2) The *encephalitic form is characterized by rapidly* developing coma rapid stertorous breathing a petechial but not massive purpuric rash and normal blood pressure (3) The *mixed encephalitic-adrenal* form is a combination of the two forms characterized by early deep coma purpura and low blood pressure Occasionally the pituitary gland may be damaged Despite all efforts these illnesses usually are rapidly fatal

Chronic meningococcemia is an infrequent form of meningococcal infection in which episodes of fever of a few days duration recur at intervals of days weeks or months Chills and arthralgic symptoms may accompany the bouts Lesions of the skin or other characteristic signs may be absent or evanescent making diagnosis difficult Repeated cultures of the blood may be *necessary before the meningococcus is* recovered Unless recognized and treated meningitis or endocarditis may develop

Meningitis This is the most characteristic and important of the metastatic localizations *although constituting numerically* a small percentage of the total meningococcal infections The *onset and symptoms* in

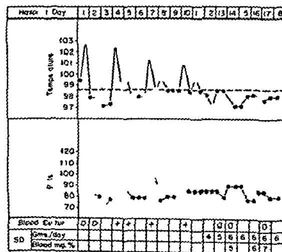


FIG 22 Meningococcemia without meningitis in a 24 year-old male due to *Neisseria intracellularis* group II treated with sulfadiazine

factors—increased intracranial pressure and meningeal inflammation—are responsible for most of the characteristic clinical findings

The reasons for limitation of meningococcal infection to the nasopharynx and the blood in some persons or for its extension to other sites of the body particularly the meninges in other persons are not clear

Chemical alterations in meningococcal infections may be profound Presumably they are initiated and maintained by metabolic and endotoxic substances from the bacterial cells together with the chemical by products of damaged tissue cells responsible for the phenomena of inflammation Hemorrhagic manifestations are due to vascular damage Other changes are similar to those in acute sepsis namely dehydration reduction in blood volume altered *acid base equilibrium from differential loss* of acid or base negative nitrogen balance and fever Meningismus may develop coincident with a relative increase in the ratio of the chlorides in the cerebrospinal fluid to the blood chlorides In severe or overwhelming infections cyanosis circulatory collapse and other signs of shock may develop probably because of the combined action of bacterial endotoxins and tissue anoxia If fluid intake is adequate there is no decrease in plasma volume no fall in plasma protein concentration and no abnormal increase in capillary permeability to protein Alterations in the blood similar to those of adrenal insufficiency such as low sodium elevated potassium low chloride and hypoglycemia may be found and *are consistent with an inadequacy of cortical secretion* resulting from damage to the adrenal cortex

Symptoms The clinical manifestations of meningococcal infections can most conveniently be described by considering successive stages in the pathogenetic sequence namely infection of the upper respiratory *tract bacteremia and meningitis or other* metastatic localization It should be emphasized however that this sequence of infection may not always be apparent clinically the infection may extend so rapidly that the symptoms and signs of all the stages coexist in a given patient at the time he is first examined or there may be such variations in the intensity of the symptoms *referable to a single* aspect of the disease that other aspects are overlooked

Infection of the upper respiratory tract is numerically the most frequent type of meningococcal infection In the majority of patients however symptoms are absent or inconsequential and infection can be detected only by culture of the nasopharynx *In the* remainder dryness or slight discharge from the nose postnasal drip soreness of the throat and suffusion of the conjunctivas may be present Physical examination reveals congestion or injection of the mucous membranes of the nose and pharynx discharge from the sinuses and rarely redness and edema of the tonsils Exudate and regional adenopathy are ordinarily absent Approximately 75 per cent of patients with generalized meningococcal infection give a history of preceding or coexisting nasopharyngitis It has been postulated that in some of these patients the symptoms are due to infection with a virus although the nature of such a virus has not been determined

Meningococcemia Bacteremic forms of meningococcal infections vary greatly from acute fulminating illnesses of a few hours duration to indolent chronic infections lasting weeks months or even years The progress of the infection may be steady and constant or there may be relapses and recrudescences at varying intervals

The commonest type of meningococcemia is a relatively mild acute or subacute infection Prodromal *symptoms* are ordinarily absent with the possible exception of those of a mild upper respiratory infection The onset is usually sudden with feverishness chilliness occasionally frank chills which may be recurrent malaise myalgia and apathy The presenting symptoms may be any of the above but not infrequently the *initial complaint will be recurrent* fever rash arthralgia acute polyarthritis gastro intestinal upsets characterized by nausea and vomiting or occasionally monarthritis or conjunctivitis The symptoms persist and often become exaggerated as the disease progresses The fever may be remittent and irregular with spikes to 102 or 103° F or it may be intermittent in quotidian tertian or quartan fashion (Fig 22) The pulse is full and strong with a rate proportionate to the fever Respirations are usually normal or only slight elevated

The most striking feature *on physical examination* is the rash which is present in the majority of patients particularly during epidemics It appears soon after onset and may take a variety of forms although the commonest lesions are petechial or purpuric measuring in diameter from 1 or 2 mm to a centimeter and are pink to reddish blue in color (Fig 23)

Early in the disease there may be a general ized mottled erythema which appears dusky if the patient is slightly cyanotic yellowish pink macules simulating the "rose spots" of typhoid wheals or nodules resembling erythema nodosum may appear before petechiae and ecchymoses Careful search in strong daylight may be neces sary to detect the early lesions Occasion ally vesicular pustular or bullous lesions are present superficial or deep ulcerations may result A common site for the lesions first to appear is about the wrists and ankles but any area of the body may be involved including the conjunctivas and the mucous membranes The hemorrhagic lesions fade to a brown rusty color three or four days after their appearance new crops may appear often following chills so that the rash may present a varied appearance

Other physical findings with the ex ception of splenomegaly are inconstant *Herpes labialis* is found in about 10 per cent of the cases Unless meningismus de velops symptoms referable to involvement of the central nervous system are absent The symptoms of metastatic localizations are usually self-evident depending on the site involved

Laboratory examinations serve to estab lish the final diagnosis Leukocytosis vary ing from 12 000 to 40 000 cells per cu mm is almost constantly present From 80 to 90 per cent of the cells are neutrophils Occasionally intracellular diplococci may be seen within the cells on a stained smear of capillary blood or of blood obtained di rectly from a skin lesion Cultivation of meningococci from the blood furnishes final etiological proof It should be emphasized that repeated cultures of the blood may be necessary to detect the meningococcus and that growth of the organism in liquid cul ture medium may be delayed Other labora tory examinations give normal findings or results compatible with any febrile illness

The subsequent course is dependent on therapy although approximately 20 per cent of the patients recover spontaneously after several weeks or months Any of the complications and sequelae of meningococ cal infections may develop

Acute fulminating meningococcemia dif fers from the milder form chiefly in the rapidity of its progress and its overwhelm ing character The onset is often abrupt and represents a dramatic departure from normal health with a shaking chill severe headache dizziness or vertigo collapse or unconsciousness Three forms may be dif ferentiated (Banks) (1) The *adrenal* form is characterized by massive purpura low blood pressure clear mental condition rapid quiet respiration and overwhelming bacteremia The extensive rash (Fig 24) involves skin and mucous membranes as well as internal organs classically the adrenals The temperature may be sub normal normal or slightly elevated Within a few hours circulatory collapse develops Adrenal hormone replacement therapy may help to sustain these patients (2) The *encephalitic* form is characterized by rap idly developing coma rapid stertorous breathing a petechial but not massive pur puric rash and normal blood pressure (3) The *mixed encephalitic adrenal* form is a combination of the two forms character ized by early deep coma purpura and low blood pressure Occasionally the pituitary gland may be damaged Despite all efforts these illnesses usually are rapidly fatal

Chronic meningococcemia is an infre quent form of meningococcal infection in which episodes of fever of a few days dura tion recur at intervals of days weeks or months Chills and arthralgic symptoms may accompany the bouts Lesions of the skin or other characteristic signs may be absent or evanescent making diagnosis dif ficult Repeated cultures of the blood may be necessary before the meningococcus is recovered Unless recognized and treated meningitis or endocarditis may develop

Meningitis This is the most character istic and important of the metastatic local izations although constituting numerically a small percentage of the total meningococ cal infections The *onset and symptoms* in

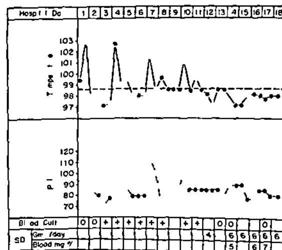


Fig 22 Meningococcemia without meningitis in a 24 year-old male due to *Neisseria intracellularis* group II treated with sulfadiazine



FIG 23 Common skin lesions in meningococcal infection (Courtesy of Dr Worth B Daniels)



FIG 24 Skin lesions in fulminating meningococcemia (Courtesy of Dr Worth B Daniels)

many cases may be indistinguishable from those of generalized infection in other cases the evidences of meningeal involvement predominate and in yet others both groups of symptoms appear to develop simultaneously even though there may be great variations in intensity and severity In addition to the manifestations of sepsis and the rash patients with meningitis present symptoms and signs of inflammation and irritation of the meninges pain in the neck and back on forward flexion of the head muscular spasm stiff neck retraction of the head or even opisthotonos the presence of Kernig s and Brudzinski s signs hyperesthesia hyperirritability and exaggerated reflexes Inequality of reflex response is not usual but may be found Involvement of cranial nerves may produce strabismus and deafness As the result of

increased intracranial pressure severe head ache nausea vomiting dilated or irregular pupils engorgement of the veins of the fundi choking of the disks irregular slow pulse and moderately elevated blood pres sure may be prominent findings Cheyne Stokes or Biot s types of respiration may develop As the infection progresses rest lessness and irritability may be succeeded by delirium or by convulsions of generalized or jacksonian type or the patient may be come greatly depressed then somnolent and finally stuporous and comatose In in fants the signs of meningitis may be no more than refusal of feedings vomiting or regurgitation diarrhea irritability and fever Convulsions and bulging of the fon tanelles if present are extremely helpful signs

Lumbar puncture reveals slightly turbid to cloudy cerebrospinal fluid under a pres sure of 250 to 300 mm or more of water The total cell count is elevated often to several thousand per cubic millimeter and the great majority of the cells are neutro phils Intracellular and extracellular diplo cocci can be found in variable numbers in stained smears of the sediment after cen trifugation The total protein in the cerebro- spinal fluid is increased and occasionally the fluid will clot after removal The sugar content is reduced Meningococci may be grown from the fluid by proper cultural methods

The course is extremely variable and is greatly influenced by therapy In untreated cases the temperature is so erratic that no typical fever curve can be described the symptoms persist and progress to early death or to chronic meningitis and delayed death or severe sequelae

Complications The complications of me ningococcal infection and meningitis in clude intercurrent infection metastatic localizations and mechanical lesions in the central nervous system They may develop during the acute stage or later in the course Intercurrent infection of the respiratory tract due to agents other than the meningo coccus may occur such as otitis media bronchopneumonia pleurisy herpes and influenza Bacteremic or metastatic com plications include conjunctivitis panoph thalmitis or other types of ocular infection otitis polyarthritis purulent monarthritis (usually a late complication) pneumonia pleurisy pericarditis endocarditis myo carditis with cardiac enlargement and electrocardiagraphic changes orchitis epi didymitis jaundice hepatorenal failure transient albuminuria and hematuria and adrenal hemorrhage Infection in the cen tral nervous system may produce the complications of transient paralyses hemi plegia neuroradiculitis encephalitis en cephalomyelitis change in mentality glycosuria convulsions cranial nerve in volvement cerebral thrombosis and brain abscess Organization of exudate in the ventricular channels and the subarachnoid space may mechanically obstruct the flow of cerebrospinal fluid and result in hydro- cephalus The accumulation of subdural fluid of high protein content which may be encapsulated and resemble a subdural hematoma is a not infrequent complica tion in infants and young children Com plications resulting from therapy may also occur

Permanent sequelae may result from al most any of the complications but the com monest are deafness ocular palsies blind ness changes in mentality psychoses and hydrocephalus

Diagnosis The diagnosis of *meningococ cal infection* depends primarily on differen tiation from other acute systemic infections and other types of meningitis In any case final confirmation of the diagnosis must be based on bacteriological identification of the meningococcus During an epidemic all cases of fever of unknown cause and abrupt onset of marked prostration with or without fever of petechial or purpuric rash of drowsiness or coma and of men ingitis should be treated as meningococcal infections even though organisms are not found in initial smears and cultures

Meningococcal infections in the early stages may resemble any acute systemic in fection In sepsis due to pyogenic organ isms such as staphylococci or streptococci there may be a preceding upper respiratory infection recurrent fever malaise arthral gia and leukocytosis A rash similar to that of meningococcemia may rarely be present in such cases Final differentiation is ac complished by isolation of the organisms from the blood Meningococcal infections must also be differentiated from the acute exanthemata typhus typhoid and other en teric fevers subacute bacterial endocarditis influenza rheumatic fever and brucellosis

The diagnosis of meningococcal menin gitis requires differentiation from meningis mus other forms of bacterial meningitis viral infections of the central nervous sys tem myeloencephalitis due to bacterial toxins (tetanus botulinus) or chemicals and noninfectious processes such as sub

arachnoid hemorrhage cerebral hemorrhage or thrombosis diabetic coma and uremia

In the majority of cases of *meningococcal meningitis* diagnosis is readily established by identification of the specific diplococcus in others the etiology may not be easy to determine when the patient is first seen but a number of procedures helpful in differentiation can be carried out The usual medical history should be obtained including a careful inquiry regarding recent localized infections and trauma to the head since these predispose to the secondary purulent bacterial meningitides Physical examination should include a careful search for diseases of the eyes and the upper respiratory passages and sinuses evidence of injury to the head and foci of infection in addition to thorough general and neurological examinations Complete blood counts should be made and cultures of the blood obtained Any foci of infection should likewise be cultured Urinalysis and determination of the blood nonprotein nitrogen aid in differential diagnosis and may indicate precautions to be observed in therapy

Lumbar puncture using aseptic technique should be performed as soon as possible and before chemotherapy is instituted After the initial pressure is determined cerebrospinal fluid should be removed slowly until the pressure is reduced to approximately normal levels The dynamics of the cerebrospinal fluid can then be determined by jugular compression to indicate the presence or absence of block or sinus thrombosis Examination of the cerebrospinal fluid should include the following appearance total cell count differential leukocyte count determination of sugar and protein examination of stained smears and cultures The chlorides may be determined if desired If no organisms are seen in the initial smears they may often be found in smears repeated after incubation of some of the fluid overnight

A tentative diagnosis can usually be made on the basis of a Gram stained smear the differential cell count and the sugar content of the cerebrospinal fluid If organisms are seen on the smear they may frequently be recognized by their morphology and staining reactions Caution should be exercised at this point however since even experienced personnel may be misled by overdecolorized or dead gram positive diplococci or other bacteria Final diagnosis depends on typing or culture and in the case of group I and IIα meningococci a direct quellung test may give immediate identification The leukocytes are almost entirely neutrophils in all the bacterial meningitides except syphilitic or tuberculous meningitis In the latter exceptions as well as in viral infections (lymphocytic choriomeningitis poliomyelitis and the viral encephalitides) mononuclear cells predominate except in the earliest stages of illness The sugar content is low in bacterial meningitides but is normal in viral infections In meningismus the fluid is usually normal with the exception of a relatively low protein and chloride content Erythrocytes and leukocytes are found in the proportion of their occurrence in blood in cases of subarachnoid hemorrhage The history other physical findings and special laboratory tests serve to differentiate myeloencephalitides due to toxins or chemicals

Prognosis The present prognosis in meningococcal infections is enormously improved because of the efficacy of the sulfonamides as therapeutic agents In untreated cases of meningococcemia and meningitis the mortality in the past has varied from 20 to 90 per cent averaging about 70 per cent after the introduction of serum therapy it averaged approximately 50 per cent Since the introduction of the sulfonamides the case fatality rate has been reduced to 10 to 15 per cent Age is an important factor in prognosis since the greatest mortality despite adequate therapy occurs in patients less than two years and more than forty years of age In the Army during World War II the over all mortality was slightly less than 5 per cent and in some series of several hundred cases even less than 1 per cent In addition to a favorable age distribution in the Army the excellent physical condition of the patients early diagnosis and prompt therapy are responsible for these remarkable figures The prognosis must still be guarded in the acute fulminating cases with abrupt onset extensive cutaneous manifestations and circulatory collapse In spite of intensive therapy such illnesses usually terminate fatally Relapses recurrences and complications have been greatly reduced by chemotherapy and the prognosis for complete recovery is good The commonest permanent sequelae with adequate chemotherapy have been deafness cranial nerve paralyses mental deficiency and less frequently blindness and hydrocephalus

Treatment Sulfonamides are the agents of choice in the treatment of meningococcal infections The majority of cases treated adequately show marked and dramatic im

provement within forty-eight hours The meningococcus is highly susceptible to all the various derivatives but sulfadiazine is preferred because of its proved efficacy and low toxicity

Patients with acute meningococcemia respond promptly to sulfadiazine given in an initial dose of 4 gm followed by 1 gm every four hours Oral administration is usually feasible parenteral administration as described below may be advisable initially if vomiting is frequent and persistent The drug should be continued for two to five days after clinical and symptomatic recovery In chronic meningococcemia more prolonged therapy may be required

In cases of meningitis chemotherapy should be instituted as soon as the diagnosis of meningitis has been established and the proper cultures obtained Parenteral administration of the drug is preferable for the first dose even though oral administration may be possible because of the rapidity with which an effective concentration is attained in the blood The initial dose of 0 05 to 0 1 gm of sodium sulfadiazine per kg of body weight (or approximately 3 5 to 6 gm) should be given intravenously as a 0 5 per cent solution in physiological saline The maintenance of an alkaline urine to prevent the precipitation of sulfadiazine (and its acetyl derivative) in the renal tubules and urinary tract has been advocated by some clinicians Usually the urine will be rendered alkaline if the initial dose of sodium sulfadiazine (approximately 5 gm in an adult) is administered intravenously dissolved in 1000 ml of M/6 sodium lactate solution The subsequent doses of sodium sulfadiazine may be given intravenously in 500 ml of M 6 sodium lactate solution If the patient is unable to retain oral medication therapy should be continued by giving the same total amount daily in three equally divided doses administered intravenously at eight hour intervals or in two divided doses given subcutaneously at twelve hour intervals Frequent determinations of the sulfadiazine concentration in the blood should be made to prevent overdosage A concentration of 10 to 12 mg per 100 ml is desirable Concentrations above 15 to 20 mg per 100 ml are not advisable since complications may result After the first two days of therapy the majority of patients will tolerate oral administration The same daily dose should be given in equally divided amounts at four or six hour intervals When the sulfadiazine is administered by mouth it is necessary to give approximately 15 gm of sodium bicarbonate in divided doses each day in order to maintain an alkaline urine Therapy should be continued for two to five days after complete clinical recovery Dehydration should be corrected by the administration of approximately 3 liters of physiological solution of sodium chloride or for the average adult 6 per cent of the body weight The additional daily intake should be sufficient to ensure a urinary output of more than 1000 ml approximately 3 liters will be necessary for the average person half of which may be given as a 5 per cent solution of dextrose Serum therapy is no longer used in the treatment of meningococcal infections

Patients with acute fulminating meningococcemia and meningitis should be treated intensively and promptly without awaiting cultural confirmation of the diagnosis Sodium sulfadiazine should be administered parenterally as outlined above Penicillin may also be given Supportive therapy directed toward the correction of adrenal insufficiency should be instituted if circulatory collapse seems imminent or has occurred (Cassidy) Optimal results should be produced by the administration of large doses of cortisone or hydrocortisone preferably intravenously together with intravenous norepinephrine to maintain blood pressure within normal limits (for further details see later section on Treatment of Adrenal Crisis) An intravenous infusion of 1000 to 1500 ml of physiological solution of sodium chloride with 10 per cent glucose should be given immediately Additional fluid may be given to correct dehydration but an excess should be avoided Oxygen therapy should be instituted and maintained as long as cyanosis or dyspnea is present Blood transfusions have not been shown to be of definite value in this type of circulatory failure

Penicillin has been used in the treatment of meningococcal infections but the results are less satisfactory than those obtained with sulfonamides unless such large doses as 1 000 000 units of sodium or potassium penicillin every two hours intramuscularly are employed (Lepper and others) This treatment schedule causes great discomfort to the patient and may increase the risk of serious reactions to the drug Penicillin can not be considered as the equivalent of the sulfonamide drugs For most patients sulfonamide drugs are preferable because of their powerful antimeningococcal action their ease of administration their demonstrated effectiveness and their low toxicity

Penicillin may be of value however in patients who are sensitive to the sulfonamide drugs and possibly as an adjunct to chemotherapy in overwhelming infections Successful therapy of meningococcal infections has been reported with other antimicrobial drugs Apart from situations in which sulfonamides are contraindicated however there are no demonstrable advantages in their use In any event therapy should be continued until clinical and bacteriological recovery has occurred

Certain laboratory tests such as determinations of the sulfonamide concentration in the blood hematological examinations and urinalysis should be made as aids in controlling therapy A concentration of 5 to 15 mg of sulfadiazine per 100 ml should be maintained in the blood the concentration of drug in the cerebrospinal fluid will be approximately one third lower Repeated determinations of hemoglobin total and differential leukocyte counts and urinalyses aid in the early detection of deleterious reactions to chemotherapy The level of non protein nitrogen in the blood should be determined frequently if the initial concentration is abnormally high or if hematuria or anuria occurs Blood cultures should be repeated if the fever persists since continued bacteremia suggests the presence of endocarditis or other metastatic localization Additional lumbar punctures are indicated if there is persistent increased intracranial pressure failure to respond to adequate therapy or relapse

Symptomatic and supportive treatment is as essential for patients with meningococcal infections as for those suffering from other severe infections Sedation should be minimal yet sufficient to assure adequate rest one of the barbiturates chloral hydrate or paraldehyde is preferred Approximately a month of convalescence will be required for complete recovery of the usual case and even longer for severe illnesses

The *therapy* of the *complications* of meningococcal infection is primarily that of the underlying disease together with local or supportive measures as indicated Should fever or signs of meningeal irritation recur the most probable causes are recurrence of infection with the meningococcus drug fever or infection due to another organism Examinations of the cerebrospinal fluid and blood should be repeated If meningococcal infection has recurred the same treatment should again be instituted

Prevention Administration of as little as 2 gm of sulfadiazine will temporarily eradicate meningococci from the nasopharynx Mass administration of the drug to both closed and open populations has accordingly been advocated as a control measure during epidemic periods and has apparently been successful (Macchiavello El Sayed and Rahman) Isolation of patients with meningococcal infections is nc necessary after twenty four hours of adequate therapy with sulfonamide drugs since the organisms are eradicated from the respiratory tract within this period Such is not the case however when the other antimicrobial drugs are used

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Bacillary Diseases

Hemophilus Infections

PERTUSSIS

(Whooping Cough)

Definition Pertussis is an acute respiratory infection caused by *Hemophilus pertussis* Typically it consists of an attack of severe spasmodic coughing followed by a sudden forceful inspiration (the whoop) Thick ropy mucus is often expelled by coughing or by vomiting at the end of a paroxysm

History Although the earliest reference to the disease was probably made by Moulton in 1540 De Baillou in 1578 is credited with the first classic description of pertussis Modern knowledge of the disease dates from 1906 when Bordet and Gengou identified the causative agent

Incidence Pertussis is sporadic and endemic to the more thickly populated com

munities throughout the world Epidemics prevail at intervals of two to four years Though cases occur regularly during the summer months they are more numerous in winter and spring when complications are likewise more frequent The peak of the incidence in the southern states occurs in May in the North in January or February It appears to be more frequent among females The communicability rate is high resembling that of measles and varicella In family exposures it approximates 85 per cent

Although pertussis occurs at all ages it is decidedly a disease of early life About 85 per cent of all cases occur in children less than seven years of age and about one half of these are found in infants less than two years of age Though maternal immunity may be passively conferred upon the newborn in certain instances infants younger than six months of age are very susceptible and are subject to a high mortality

Etiology *Hemophilus pertussis* discovered by Bordet in 1906 is the causative agent It is a small gram negative ovoid bacillus about 0 5 μ in length It occurs in the respiratory tract in great numbers during the catarrhal stage of the disease but rapidly disappears during convalescence Carriers are rare

The disease has been produced experimentally by inoculation of suitable animals and man with pure cultures of the organism Specific humoral antibodies result from the natural infection and from injection of specific vaccine Immunity usually follows an attack of pertussis but a few bacteriologically proved instances of second attacks have been observed

Other organisms such as *Hemophilus influenza* *Brucella bronchiseptica* and *H parapertussis* may cause infections resembling whooping cough The last two of these are related to *H pertussis* on the basis of a common minor antigen

Morbid Anatomy Catarrhal infection in the epithelium of the respiratory tract is always present Here clumps of *H pertussis* occur and beneath them develops the essential lesion of necrosis of the midzonal and basal portions of the bronchial epithelium with infiltration by polymorphonuclear leukocytes Peribronchiolitis progresses into typical interstitial pneumonia Edema and hemorrhage occur early as parenchymal lesions Mucus pus and cellular debris within the alveolar spaces usually result from secondary infection although *H pertussis* alone can produce the entire lesion

In severe cases the brain is congested and contains punctate or larger hemorrhages In rare instances encephalitis with cortical atrophy occurs

Pathological Physiology The essential departures from the normal physiological state observed in pertussis are (1) those related to disturbances in nutrition (2) those resulting from changes in the pulmonic circulatory system and (3) those referable to the central nervous system

Loss of appetite and vomiting cause weight loss Excessive vomiting may produce gastric tetany In infants diarrhea frequently occurs Dehydration starvation and emaciation impair nutrition to the extent that fatal secondary infections develop

Irritation of the mucous membranes of the trachea and bronchi provokes the paroxysm Obstruction of the lower air passages by mucous plugs induces atelectasis which along with interstitial pneumonia prevents proper oxygenation of the blood According to Regan and Tolstoouhov a state of uncompensated acidosis results Enlargement of the right side of the heart may result from increased impediment of the pulmonary circulation

Anoxemia probably causes convulsions in many instances Infancy pneumonia and severity of the paroxysms are important factors Cerebral congestion edema hemorrhage and encephalitis are responsible for convulsive and other types of disturbances in the central nervous system There is evidence that hypersensitivity is a causative factor in pertussis encephalitis In rachitic infants convulsions may be due to tetany

Symptoms The incubation period though variable is usually from seven to fourteen days In a series of 1123 cases Lawson found the mean duration of the period to be thirteen days The course of the typical disease is six weeks in length representing three stages the catarrhal spasmodic and convalescent each lasting approximately two weeks

Catarrhal Stage This period begins with a mild cough usually nocturnal which progresses in intensity and soon becomes diurnal The mean duration of this period according to Lawson is eleven days Coryza and sneezing are usually present and the appetite fails The cough later resembles that of bronchitis At this stage the physician is frequently consulted In rare instances hoarseness is present and occasionally the disease begins with the features of acute obstructive laryngitis There is often suffusion of the conjunctiva

Spasmodic Stage After about ten to four

teen days the cough becomes so aggravated that it occurs in series of explosive efforts in which the face becomes congested often cyanotic the tongue protrudes with each cough and the patient appears to strangle Finally the attack ends with a sudden forceful inspiratory crow or whoop Large amounts of thick ropy mucoid material are coughed up swallowed or vomited Perspiration congestion of the neck and scalp veins mental confusion and exhaustion may follow the more severe paroxysms Infants particularly may become so cyanotic and exhausted that they may require artificial respiration

Excitement sudden thermal changes swallowing inhalation of irritating fumes tobacco smoke or even the occurrence of a paroxysm in a nearby patient may excite a spell of coughing If a plug of mucus remains in contact with the hyperesthetic mucous membrane of the respiratory tract recurrent paroxysms very likely follow until it is dislodged Epistaxis often occurs when the spasms are severe Subconjunctival hemorrhages and edema of the lower eyelids occur frequently in cases with severe coughing

Convalescent Stage The number and severity of the paroxysms gradually decrease vomiting becomes less frequent and the disease thus progresses into the stage of decline or convalescence During this period the hilar and basilar rhonchi gradually disappear For a period of weeks or months an intercurrent infection may cause the major symptoms to reappear even to the point of resembling a new attack

It must be remembered that pertussis is a variable disease and may exist in a mild atypical form The entire course may last only a few days Proved cases have been known to last but from seven to fourteen days Vomiting and the classic whoop may never occur Very young infants particularly may have choking and cyanotic spells without the whoop

Complications and Sequelae Bronchopneumonia is by far the most important complication This is usually interstitial in type Lobar pneumonia is rarely seen but occasionally confluent bronchopneumonia produces a lesion which clinically resembles that seen in the lobar type Atelectasis is common because the blocking of a bronchus with mucus resulting in collapse of a portion of the lung and frequently leading to the erroneous diagnosis of pneumonia Vesicular and interstitial emphysema occurs in practically all severe cases Emphysema of the cellular tissue of the mediastinum may result from rupture of air blebs on the surface of the lung From the mediastinum the air may find its way into the subcutaneous tissues of the neck and even spread to other parts of the body Cases with widespread subcutaneous emphysema are usually fatal In one case of this type which later came to anatomical examination there was hyperleukocytosis of 257 000 cells per cubic millimeter Pneumothorax may occur Bronchial asthma and bronchiectasis may result from an atack of pertussis An existing tuberculous lesion may spread during the disease although the effect of pertussis on tuberculosis is probably not as disastrous as was formerly believed Unresolved pneumonia and pulmonary fibrosis are of common occurrence Cardiac dilatation particularly of the right side is observed It is most commonly associated with diffuse pneumonic involvement

Otitis media is frequently encountered and is due to secondary invading organisms Because of the tendency to suppurate the ears require the careful attention of the attending physician

The hemorrhages of pertussis are mechanical in origin resulting from the venous congestion associated with severe coughing Epistaxis and hemorrhage of the bulbar conjunctivas are common Blood tinged sputum is a result of small erosive lesions in the trachea which occur during a paroxysm Hemorrhage of the brain has been reported

The most common neurological complication of pertussis is convulsions They occur in about 8 per cent of hospitalized cases and are especially common in infants The cerebrospinal fluid of those suffering from convulsions is usually normal

Other neurological complications of pertussis are epilepsy mental retardation spastic paralysis myelitis and temporary or permanent visual disturbances

Hernia usually umbilical and prolapse of the rectum are results of severe straining associated with the cough Ulcer of the frenum occasionally results when the tongue is repeatedly thrust over the edge of the lower incisor teeth during the paroxysms

Diagnosis Typical pertussis in the paroxysmal stage can be readily recognized In the catarrhal period and in the atypical abortive form it is difficult to diagnose Pertussis should be suspected in a person suffering from a cough of a week s duration if examination of the nose throat and chest reveals no apparent cause for it History of exposure may not be elicited

The physician may be obliged to defer diagnosis until the cough becomes more definite In such instances the patient should be isolated and a culture taken if the facilities are available In doubtful cases inquiry should be made concerning previous injections of vaccine since mild atypical cases may occur as a result of the partial immunity thus conferred

The most valuable of the laboratory diagnostic tests consists in the isolation of the organism from the upper respiratory tract This may be accomplished by the cough plate technique or by the nasal swab method Bacteriological diagnosis is particularly applicable during the catarrhal period when positive cultures may be expected in from 70 to 90 per cent of the cases Only positive cultures are significant A single negative culture does not exclude the disease

A characteristic change in the leukocytes occurs during the late catarrhal or early spasmodic stage This consists in a definite leukocytosis of from 15 000 to 40 000 white blood cells per cubic millimeter reflecting progressive increase in the absolute number of lymphocytes Occasionally extreme degrees of hyperleukocytosis occur usually in cases complicated by pneumonia This change in the leukocytes is probably due to direct stimulation of the hematopoietic tissues by *H pertussis* Failure to find this blood change does not constitute conclusive evidence against the existence of the disease

In certain instances the finding of a significant titer of humoral antibodies in an unvaccinated patient may suggest recent infection with *H pertussis* Tests for agglutinins and complement fixing and mouse protective antibodies may be made with the patient s serum Unfortunately humoral antibodies do not appear until the paroxysmal stage hence they are of little diagnostic value early in the disease Attempts to develop a diagnostic skin reaction with various toxins and fractions of the organism have not been entirely successful

Prognosis During the period 1920 to 1953 the mortality from pertussis in the United States decreased from 12 5 to 0 2 per 100 000 population In 1950 the fatality rate for the United States Registration Area was 0 93 per cent while in New York City (1951 1954) it was only 0 13 per cent The highest death rate is in rural rather than urban areas The younger the patient the more grave is the prognosis

Prognosis should include recognition of serious sequelae as well as the immediate fatality rate

Treatment *General Measures* Normal room temperature and bed rest are desirable Good nursing and hospital care are important in the care of seriously ill infants Excitement and extreme changes in temperature provoke coughing When vomiting is excessive small frequent feedings are advisable Obstruction of the respiratory tract by excessive mucus may be relieved by careful suction

Oxygen should be given to all patients with increased respiratory rates with or without cyanosis for it is one of the most important therapeutic agents for this disease Small blood transfusions are indicated in cases complicated by anemia A roentgenogram of the lungs and a tuberculin test should be obtained during convalescence

Medication Codeine paregoric and phenobarbital are useful sedatives Rectal instillations of a mixture of 2 to 8 ml of ether in 15 ml of olive oil every six to eight hours as necessary are effective for the control of severe paroxysms The subcutaneous injection of 0 008 to 0 016 gm of sodium phenobarbital may prove helpful for the control of convulsions Magnesium sulfate (0 06 gm per kg of body weight) may be injected intramuscularly for the same purpose

Specific Therapy Hyperimmune serum is indicated in severe cases Hyperimmune human serum (20 to 40 ml) or the gamma globulin (5 to 10 ml) prepared from it serves similar purposes

Chloramphenicol and the tetracyclines are about equally effective in dosages of 50 mg per kg of body weight per day divided into four doses Because of its potential toxic effect on the bone marrow chloramphenicol should be used only in severe cases with careful observations of the blood count

Penicillin is obviously indicated for the treatment of pyogenic complications

In a previously vaccinated person additional injection of vaccine early in the disease is immunologically sound treatment

Prevention Young infants should be carefully protected from exposure to pertussis The period of infectivity is about six weeks but the catarrhal stage is most dangerous

Active immunization should start at or before the third month of age The initial course of vaccine should be given in three monthly injections The total dose should be 12 units contained in not more than 96 billion organisms in saline or 48 billion

organisms in alum precipitated preparations Stimulating injections (2 units each) should be given every two years until school age

To the exposed nonimmunized infant passive protection may be given by the intramuscular injection of hyperimmune human serum (10 to 20 ml) or gamma globulin prepared from hyperimmune human serum (2 5 to 5 ml)

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HEMOPHILUS INFLUENZAE INFECTIONS

The influenza bacillus has played two major roles in human infections (1) as a secondary invader in the influenza virus pandemic of 1918—Jordan has summarized the evidence for this influence and (2) as a primary agent in pyogenic infections

PRIMARY H INFLUENZAE INFECTIONS

Encapsulated *H influenzae* Although six specific types of *H influenza* a b c d e and f were differentiated by Pittman type b is responsible for almost all primary severe infections caused by influenza bacilli The pathogenic potentialities of encapsulated *H influenzae* as a primary agent are greatly modified by the age of the host The severe pyogenic infections occur almost exclusively in infants and children The decline in incidence with increasing age has been shown by Fothergill and Wright to be closely related to a greater bactericidal power of the blood of older subjects This immunity is apparently the result of past contact with the organism

In Childhood Type b *H influenzae* is one of the commonest causes of severe infections in infants and children (Alexander and others 1942) Pediatricians are now familiar with several patterns of illness all of which are preceded by a nasopharyngitis The complications result from remote seeding consequent to a bacteremia as well as from spread to the ears paranasal sinuses larynx and lungs Of the severe infections meningitis obstructive laryngitis pyarthrosis and pneumonia occur *most frequently*

In Adults Immunity to these severe *H influenzae* infections while exhibited by most adults is not uniformly present Type b *H influenzae* pneumonia meningitis obstructive laryngitis and pyarthrosis are seen in adults but they occur very rarely

PNEUMONIA *H influenzae* type b pneumonia cannot be differentiated from pneumococcal pneumonia by clinical signs or the ordinary laboratory examinations The lesion may be lobar in distribution the blood shows a moderate leukocytosis and the erythrocyte sedimentation rate is significantly elevated Following adequate sulfonamide therapy the subsidence of infection is as prompt as in the average patient with pneumococcal pneumonia Penicillin in the usual dosage is not effective and on this basis *H influenzae* pneumonia may at times be erroneously classified as viral pneumonia

MENINGITIS *H influenzae* is the most frequent cause of meningitis in infants and children Prior to 1938 the mortality rate was virtually 100 per cent Patients with *H influenzae meningitis do not exhibit* clinical signs which can be distinguished from those of other varieties of pyogenic meningitis The clinical signs and changes in the cerebrospinal fluid vary with the stage of the disease and the severity of infection However prompt identification of the etiological agent can be made by bacteriological and serological procedures

OBSTRUCTIVE LARYNGITIS WITH EPIGLOTTITIS One form of severe rapidly progressing laryngeal obstruction is caused by *H influenzae* Lemierre was the first to separate influenzal laryngitis from other forms of croup he reported its occurrence in both children and adults In children *H influenzae* laryngitis presents a characteristic history and the patient a characteristic appearance The onset is sudden and the course fulminating Mild fever and dysphagia develop during an apparently in

nocuous respiratory infection Dyspnea starts abruptly and increases within a few hours to such a degree as to make hospitalization imperative The picture is that of a prostrated child with severe laryngeal obstruction usually demanding tracheotomy The temperature is high On examination of the pharynx there is diffuse erythema often with evident edema and when the tongue is pressed downward the enlarged distorted red and edematous epiglottis is easily seen

Bacteriological Diagnosis H influenzae may usually be identified within thirty minutes when the infection is severe by the demonstration of capsular swelling of bacterial cells found in the appropriate biological fluid In patients with pneumonia or obstructive laryngitis the organisms should be sought for in a concentrated suspension of nasopharyngeal mucus they are found in cerebrospinal fluid in patients with meningitis in joint exudate in those with pyarthrosis and in the pleural exudate in empyema When such direct identification is impossible growth in special media can usually be obtained in twelve hours (Dubos) In children bacteremia is a constant feature in all varieties of severe *H influenzae* infections

Nonencapsulated *H influenzae* A primary pathogenic role of nonencapsulated *H influenzae* can seldom be established this organism in fact is found frequently (30 to 50 per cent) in the nasopharynx of normal persons of all age groups In infants it may occasionally cause meningitis or pneumonia In adults it is a rare cause of subacute bacterial endocarditis and brain abscess The Koch Weeks bacillus *H aegyptius* (Pittman) (which cannot be differentiated from *H influenzae*) has been reported as the primary agent in epidemics of conjunctivitis[4]

Treatment of *H influenzae* Infections The therapeutic efficacy of sulfonamides specific rabbit antiserum streptomycin and chloramphenicol against *H influenzae* is now well established When the infection is sufficiently mild each of these agents can bring about recovery On the other hand if the infection is severe each is limited in its therapeutic capacity the combined action of two is required for successful treatment The location duration and severity of infection govern the number of agents which shoud be used simultaneously in a given patient Experience with these agents in the various *H influenzae* clinical patterns is well documented in childhood infections only but there is every reason to believe that the methods of treatment in this age group are applicable to adults (Alexander 1954)

In obstructive laryngitis sulfadiazine alone can cure most patients after an adequate airway is established by tracheotomy Pneumonia can also be successfully treated with sulfadiazine alone However the risk of therapeutic failure is virtually eliminated by the initial use of a second effective agent chloramphenicol or a tetracycline In meningitis pyarthrosis and empyema the combined action of two drugs is indicated There are now sufficient data for comparison of three different therapeutic programs in meningitis (1) type specific rabbit antiserum and sulfonamides (2) streptomycin and sulfadiazine and (3) chloramphenicol and sulfadiazine Any of the three can be expected to cure virtually 100 per cent of the patients who are treated early in the course of the disease It has not been possible to show a significant difference in efficacy among these three pairs of agents The ease with which optimal concentrations can be maintained in the cerebrospinal fluid by either the oral or parenteral routes and the rarity of injurious effects make the combined action of chloramphenicol and sufadiazine the treatment of choice for meningitis and all other severe varieties of *H influenzae* infections When the oral route is used for chloramphenicol 200 mg per kg is given daily in four doses (not to exceed 3 gm) when parenteral administration is necessary 100 mg per kg (not to exceed 2 gm) is given each twenty four hours in three doses The dose in adults should not exceed 5 gm orally or 3 gm parenterally Parenteral administration is recommended during the first twenty four hours either by continuous intravenous drip using sulfisoxazole (Gantrisin) as the sulfonamide or by the intramuscular administration of chloramphenicol and the subcutaneous administration of the 5 per cent sodium salt of sulfadiazine

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HEMOPHILUS DUCREYI INFECTIONS

(Chancroid)

Hemophilus ducreyi was first described by Ducrey in 1889 in stained purulent material from soft chancres as minute gram negative bacilli 1 to 2 μ in length arranged in pairs chains or fish school" formations The microorganism cannot be cultivated on ordinary media By special methods however growth of *H ducreyi* is usually obtained from pus derived from infected patients provided that the lesion is not grossly contaminated by secondary invaders Typical morphology on stained smear and characteristic growth are accepted by some as adequate evidence for diagnosis of *H ducreyi* as the etiological agent Others require in addition a positive skin test autoinoculations by rubbing the lesion fluid into the scarified skin of the forearm and typical histological changes on biopsy The reliability of any one of these tests for diagnosis in a particular patient is open to question The presence of characteristic clinical features and exclusion of syphilis lymphogranuloma venereum granuloma inguinale and herpetic infections by specific laboratory tests are necessary prerequisites for diagnosis of *H ducreyi* as the causative agent

H ducreyi infection has assumed an important role as a venereal disease in the southern part of this country and in tropical regions of the world During World War I about 10 per cent of all chancres were caused by *H ducreyi* Soft chancre or chancroid produced by *H ducreyi* has a characteristic clinical appearance and history After an incubation period of two to fourteen days following sexual intercourse there appears a small red papule on the genitals or surrounding skin which in a period of a few days goes through a purulent and then necrotic stage followed by ulceration The ulcer is characterized by surrounding erythema and edema and by edges which become irregularly undermined The induration which is typical of the syphilitic chancre is absent in chancroid The lesions produced by *H ducreyi* are frequently multiple as the result of autoinoculation When untreated abscesses of the inguinal lymph nodes follow and are associated with constitutional signs

Sulfonamides are effective treatment for *H ducreyi* lesions the tetracyclines streptomycin and chloramphenicol have also been used with success However as each of the latter agents shows some action against *Treponema pallidum* their use is contraindicated unless the lesion proves resistant to sulfonamides and daily darkfield examinations on four successive days fail to demonstrate *Treponema pallidum*

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Granuloma Inguinale

Granuloma inguinale is an indolent granulomatous and ulcerative disease usually localized to the genitalia and caused by a pleomorphic coccobacillus *Donovania granulomatis* the so called Donovan body" Presumably the infection is customarily transmitted during coitus or other close bodily contact and the degree of communicability appears to be relatively low The lesion tends to be single and may rarely appear on surfaces of the body other than the genitalia Systemic infection notably with the production of arthritis or osteomyelitis has been reported Usually the lesion appears on the genitalia or in the perianal area as a relatively painless nodular infiltration which soon breaks down leaving a sharply demarcated ulcer with friable granulation tissue at the base On histological examination the lesion appears well vascularized and is the site of considerable cellular infiltration especially with polymorphonuclear leukocytes and monocytes In appropriately stained tissue scrapings the causative microbe *Donovania granulomatis* may be seen to be situated principally within the monocytes although smaller numbers of extracellular microorganisms can usually be identified The lesion spreads by direct extension is highly destructive to the skin and subcutaneous tissue and secondary infection with other microorganisms is common Rarely if sufficiently extensive the process may cause elephantiasis of the genitalia

There is nothing particularly character

istic about the lesions of granuloma inguinale and the early lesion is indistinguishable from those produced by *T pallidum* *H ducreyi* or other processes that involve the genitalia The diagnosis can be established only by appropriate microbiological techniques and these should be employed whenever the physician encounters a genital lesion (or an indolent ulceration elsewhere) that is not clearly caused by some other process Microscopy of deep scrapings or impression smears from the lesion of granuloma inguinale stained by the Wright method usually reveals *Donovania granulomatis* within the monocytes The ease with which the microorganisms can be detected varies to some extent with the age of the lesion In a relatively old lesion the scrapings should be made from the depth of the lesion and an extensive search of the smears may be necessary The microorganisms can also be cultured in medium containing chick embryo yolk by methods originally developed by Anderson and her associates Antigen prepared from capsular material of *D granulomatis* has been employed in a complement fixation reaction and in a cutaneous reaction but these have not yet been developed to the point of general application

Granuloma inguinale has been successfully treated with streptomycin chloramphenicol and the tetracyclines As initial therapy tetracycline may be employed in a total daily dosage of 2 0 gm administered by mouth in divided doses for a two week period In unusually extensive lesions it may be necessary to continue the treatment for a longer period in order to attain complete healing If relapse occurs or the lesions appear refractory to tetracycline treatment streptomycin (or dihydrostreptomycin) should be administered intramuscularly in a total daily dosage of 2 0 gm in divided doses for a two week period

With respect to the prevention of granuloma inguinale no detailed information is available It seems likely however that thorough washing of the genitals with soap and water immediately after sexual intercourse has a significant influence in reducing the probability of infection

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Diphtheria

Definition Diphtheria is an acute infectious disease caused by a bacillus *Corynebacterium diphtheriae* The primary lesion is usually located in the pharyngeal area (fauces nasopharynx or larynx) and is characterized by the formation of a grayish pseudomembrane The organism elaborates a specific soluble exotoxin which is responsible for the local cellular injury and the systemic manifestations of the disease

History Although a diphtheria like disease was described by medical writers as early as the second century A D diphtheria was first established as a clinical entity by the publication of Pierre Bretonneau s classic monograph in 1826 In 1883 Klebs described the diphtheria bacillus a year later Loeffler demonstrated its etiological relationship to the disease and in 1888 Roux and Yersin clarified the pathogenesis of the disease by their discovery of the specific exotoxin The first effective antitoxin was produced by von Behring in 1890 Schick introduced his skin test for determining susceptibility in 1913 Active immunization first introduced by Theobald Smith and by von Behring received its greatest impetus from Ramon s demonstration in 1923 that formalin treated toxin (*i e* toxoid) represented a nontoxic antigenically effective immunizing agent Today the disease occurs throughout the world In recent years morbidity and mortality rates have shown a significant decline in western Europe and North America

Etiology The causative agent of diphtheria *Corynebacterium diphtheriae* is a gram positive nonmotile nonsporulating bacillus which is characteristically club shaped and frequently beaded in appearance In stained smears the organisms are usually found arranged so as to form sharp angles with each other giving the characteristic Chinese letter appearance Diphtheria bacilli grow well on ordinary laboratory media containing peptones or tissue extracts The commonest media used are Loeffler s coagulated blood serum and potassium tellurite agar Virulent diphtheria bacilli are distinguished by the ability to elaborate and secrete a specific poisonous substance diphtheria toxin which is a true exotoxin It is the cause of the tissue necrosis occurring in the course of the clinical disease Chemically it is a complex protein but the mechanism of its action is obscure So-called nonvirulent strains of *C diphtheriae* fail to produce this toxin Freeman and others have shown that the ability to produce toxin is frequently associated with infection of the bacterial cell with a lysogenic bacteriophage which under proper conditions can convert an avirulent non toxin producing strain into a fully virulent toxin producing one Three types of *C*

diphtheriae are recognized largely on the basis of their characteristic colonial formation on potassium tellurite medium and their distinctive fermentation reactions All three types *gravis* *mitis* and *intermedius* produce the same toxin and the same clinical picture The weight of evidence at the moment suggests that *gravis* strains are found associated most frequently with epidemic diphtheria and *mitis* and *intermedius* strains with the endemic disease

Epidemiology and Immunity *Corynebacterium diphtheriae* is essentially an obligate parasite of man hence the human host represents the only significant reservoir of diphtheritic infections The organisms may be transmitted directly or indirectly from one person to another As the usual habitat of the organism is the upper respiratory tract droplet infection is probably the commonest method of spread although contamination of the hands handkerchiefs and similar objects may play an important role Discharges from extrarespiratory sites of infection (such as superficial ulcers of the skin) are infectious Although the organism may survive for a brief period outside the human body spread of infection by contaminated dust appears to be a rare occurrence A few milk borne outbreaks have been reported

Invasion and infection of the human body by the diphtheria bacillus is not always followed by the development of clinical disease More frequently the organism multiplies in the mucous membrane linings of the air passages for a shorter or longer period without causing signs of illness Presumably in such case the carrier possesses a pre existing immunity of greater or lesser degree which although it does not prevent the actual implantation of the organism does limit the amount of damage to the host s cells so markedly that no clinical manifestations develop

Immunity against the clinical disease depends primarily upon the presence of antitoxin in the blood of the infected person Although it is probable that upon occasion antibacterial mechanisms play a role in preventing the diphtheria bacillus from actually establishing itself in the throat of the human subject nothing is known concerning the nature or specificity of the reaction On the other hand recovery from an attack of clinical diphtheria is associated with the appearance of appreciable amounts of antitoxin in the blood

This antitoxin is formed in response to the direct stimulation of diphtheria toxin It has the characteristics of a true antibody it may be formed in response to either clinical or subclinical infection or as a result of artificial active immunization Although it is produced relatively slowly in response to the primary stimulation it appears rapidly and in large amounts following secondary stimuli Even though little or no antitoxin can be demonstrated at the time of the secondary stimulation it may be transferred to other persons (naturally by transplacental passage *in utero* artificially by transfusion) thereby conferring temporary passive immunity upon the recipient

Schick Test Although the accurate determination of antitoxin levels is a laboratory procedure the Schick test will usually yield valuable information concerning the immune status of an individual This test is performed by injecting into the skin of the forearm 0 1 ml of diluted diphtheria toxin A positive reaction is characterized by the development of a variable area of redness at the site of inoculation over a period of 72 to 120 hours The reaction reaches its height on about the fifth day after this it gradually fades leaving an area of brownish pigmentation which may persist for some weeks Such a positive reaction is associated with an antitoxin level in the circulating blood of less than 0 03 units of antitoxin per ml and is interpreted to mean that the patient is susceptible to the clinical disease A negative Schick reaction signifies that the blood antitoxin level exceeds 0 03 units per ml and that the subject s chances of contracting clinical diphtheria are comparatively slight The occasional negative reactor who does develop clinical illness usually has a mild attack

In actual practice the diluted toxin is injected in one forearm while the other forearm is injected with a similar amount of the same material which however has been heated to 60 C for thirty minutes in order to destroy the toxin This control is necessary in order to detect *pseudo-Schick reactions* reactions due to products of growth of the diphtheria bacillus other than the toxin itself The pseudo-Schick reaction is characterized by the development of erythema at the site of inoculation about eighteen hours after injection This increases to reach its maximum intensity at twenty four to thirty six hours and then fades gradually to disappear completely within the next seventy two hours Such a reaction connotes allergy to some component of the injected material rather than absence of circulating antitoxin in quantities adequate to confer immunity Thus four types of reaction are possible as is indicated in the accompanying table

Babies born to immune mothers will give negative Schick reactions at birth owing to the transplacental transfer of antitoxin This passive immunity wears off rapidly and by the sixth month in the absence of artificial immunization nearly all infants are susceptible to the disease as evidenced by the demonstration of a positive Schick reaction From thi point on there is a gradual rise in the proportion of persons giving Schick negative reactions as a result of natural immunization usually following subclinical infection In the absence of continued contacts with the diphtheria bacillus the antitoxin level falls to a point where the person is again susceptible to the disease

Reactions to Schick Test

TYPE OF REACTION	OBSERVATION				INTERPRETATION	
	Test 36 hr	Arm 120 hr	Control 36 hr	Arm 120 hr	Immunity	Sensitivity
Positive	–	+	–	–	Absent	Absent
Negative	–	–	–	–	Present	Absent
Pseudo	+	–	+	–	Present	Present
Combined	+	+	+	–	Absent	Present

Pathogenesis and Pathological Physiology The usual habitat of the diphtheria bacillus is the upper respiratory tract of man In a susceptible person the organism multiplies in the superficial epithelial cells of the pharynx elaborating and secreting the specific toxin in the process The absorption of this toxin by neighboring cells initiates a process of tissue necrosis which furnishes conditions favorable to the growth of the organism which in turn produces more of the toxin As the process continues it stimulates an inflammatory reaction on the part of the body leading to the formation of the typical diphtheritic membrane The absorption of toxin into the general circulation results in a degree of prostration usually out of proportion to the relatively mild appearance of the local lesion at this stage If the membrane involves the larynx and trachea either primarily or secondarily mechanical obstruction to the airway may develop and death due to suffocation may occur unless the oxygen lack is corrected by intubation or tracheotomy The soluble toxin is carried in the general circulation to susceptible organs such as the heart and cranial or peripheral nerves Cardiac failure may be the result of specific necrotic injury to the myocardium or it may be secondary to peripheral circulatory disturbances The cranial or peripheral nerve involvement is presumably due to the direct action of the toxin on the nerve cells The explanation of the relatively selective action of the toxin remains obscure

Aside from the striking picture of the local lesion the pathological changes noted in fatal cases of diphtheria are relatively nonspecific Grossly the heart liver kidneys and adrenal glands may show degenerative changes characterized microscopically by necrosis fatty infiltration and parenchymatous degeneration

Clinical Manifestations Diphtheria is characterized by a relatively short incubation period—one to four days on the average with an outside limit of one week The clinical manifestations depend *first* upon the severity of the process (which may show every gradation between a mild nearly inapparent infection and a highly malignant progressive one) and *second* upon the anatomical location of the primary lesion The more important clinical types are faucial (or tonsillar) nasopharyngeal and laryngeal Extrarespiratory forms of the disease such as ocular aural and cutaneous diphtheria do occur but in general are of less importance

In *faucial diphtheria* the process is limited essentially to the tonsillar area The onset is abrupt and is characterized by moderate fever chilliness general malaise and mild sore throat Swallowing is relatively painless The pharynx is moderately injected and dull red in appearance The pseudo membrane first appears as a thick gelatinous exudate confined to one tonsil This spreads to the other tonsil and thickens up so as to give the typical dirty white or grayish yellow diphtheritic membrane If the pseudo membrane is forcibly removed a raw bleeding surface is exposed beneath over which the membrane rapidly forms anew Tonsillar swelling is usually present and frequently there is some enlargement of the cervical lymph nodes If the tonsils are absent the membrane may be less characteristic Often the process spreads to involve the uvula and soft palate which become edematous If the process remains limited to the tonsillar area the clinical manifestations may be so mild that a definite diagnosis can be made only by isolation of the organism

Nasopharyngeal diphtheria represents a spread of the original process from the faucial area to the uvula soft palate posterior pharyngeal wall and nasal mucosa The membrane covering these areas presents a dirty yellow appearance in some instances it invades the anterior nares and actually protrudes through the external opening Occasionally the middle ear may be invaded as well Faucial edema is marked and there is usually a serosanguineous nasal discharge Enlargement of the cervical lymph nodes is almost invariably present the swelling may be so marked as to deserve the name bullneck A characteristic diphtheritic odor is usually present as well as pallor and cyanosis Marked toxemia is the rule and the patient is almost always prostrated Oliguria albuminuria weak rapid pulse and high fever are prominent features If recovery ensues sequelae are common This form of the disease should not be confused with anterior nasal diphtheria in which the disease process is limited to the anterior nares This latter is a relatively benign process with minimal toxicity and its importance is chiefly epidemiological rather than clinical

Laryngeal diphtheria usually results from the spread of infection downward from the nasopharynx although the primary lesion may be in the larynx itself It is a particularly dangerous form of the disease since the membrane and accompanying edema

produce mechanical obstruction of the air way giving rise to the classic diphtheritic croup The first symptoms are hoarseness dyspnea and a characteristic brassy cough As the obstruction increases dyspnea be comes more marked and ultimately cyanosis appears together with aphonia and expira tory and inspiratory stridor As bronchial secretions accumulate behind the obstruc tion the accessory muscles of respiration are brought into play and the spasmodic attacks of severe dyspnea gradually be come frequent and persistent Unless the airway is restored by intubation or trache otomy death by suffocation ensues Rarely the process involves the bronchial tree as well

Extrarespiratory Diphtheria Although diphtheria is usually a disease of the upper respiratory tract other parts of the body may be the site of primary or secondary diphtheritic lesions Thus wounds sores and abrasions of the skin may become secondarily infected During World War II a number of skin infections occurred among men serving in the tropics These took the form of chronic nonhealing ulcers which developed at the site of minor abrasions In the course of time a dirty grayish mem brane appeared The majority of these in fections yielded *mitis* strains on culture The relatively low percentage of sequelae suggests that the absorption of toxin from such wounds was not marked while the fact that antitoxin usually gave disappoint ing results raises the possibility that these so called tropical sores had a complex etiology

Ocular diphtheria is a rare form of the disease the conjunctivae are chiefly in volved

Diagnosis The *presumptive diagnosis* of diphtheria must be made on clinical grounds without waiting for laboratory con firmation since the importance of early specific therapy of the disease is so para mount The cardinal features pointing to the diagnosis are (1) a comparatively painless pharyngitis involving the tonsils (or tonsillar beds) and frequently the uvula and soft palate as well (2) a relative lack of redness in spite of the presence of a significant degree of edema (3) the ap pearance of the characteristic membrane in the tonsillar area and (4) moderate pyrexia In severe cases significant systemic manifestations occur in mild cases how ever the patient may feel well throughout while the throat may appear comparatively innocuous

The *laboratory diagnosis* depends upon the isolation and identification of the causa tive organism from the lesion The throat or wound swab should be taken by an ex perienced person and sent to the laboratory without delay Here a Loefflers slant a tellurite plate and a blood agar plate should be inoculated *promptly* Although experi enced workers can recognize the organism in a fair percentage of cases by smears made directly from the wound or throat swab this procedure is not recommended for the average laboratory The inoculated cultures may be inspected at the end of sixteen to twenty four hours and a pre sumptive diagnosis made on the basis of characteristic colony formation and cellular morphology Confirmatory evidence may be obtained by a study of fermentation reac tions and whenever indicated virulence tests should be carried out Other labora tory findings include a moderate leukocy tosis and a transient albuminuria in all but the mildest cases

Streptococcal tonsillitis and pharyngitis are most often confused with diphtheria In the former conditions the throat is usu ally a fiery red the tonsillar exudate thinner and lighter colored the fever higher and swallowing is markedly painful Frequently the follicles in the faucial area are quite prominent Upon occasion it may be impos sible to differentiate the two infections with out resort to laboratory means Rarely a concomitant streptococcal infection may mask the underlying diphtheritic process Other conditions which must be considered in the differential diagnosis are *Vincents angina agranulocytic angina infectious mononucleosis post tonsillectomy throat* and *exudative pharyngitis caused by an adenovirus*

Complications The most important com plications are related to the *myocardium* and the *nervous system* Signs of myocar ditis may appear as early as the second week of the disease although the usual time of onset is somewhat later They are characteristically associated with the se verer forms of respiratory diphtheria In general those cases showing early myo-cardial involvement tend to run a graver course The onset may be insidious with rising pulse of poor quality distant heart sounds premature contractions and gradual cardiac enlargement Less often cardiac failure may appear with little warning Pallor epigastric pain vomiting and circu *latory collapse are the usual signs* and symptoms Inversion of the T waves de layed conduction time bundle branch block and terminally ventricular flutter or fibrilla

tion are the commonest electrocardiographic changes noted Occasionally peripheral circulatory collapse occurs in the absence of demonstrable cardiac damage Recovery when it takes place is usually complete

Postdiphtheritic paralysis affecting the cranial or peripheral nerves is a relatively frequent complication The commonest form of cranial nerve palsy is *paralysis of the soft palate* This makes its appearance in the third to fifth week of the disease and is ushered in by the development of a nasal twang to the voice and regurgitation of fluid through the nose upon attempted swallowing Although the course is usually mild occasionally tube feeding may be required The condition tends to clear up completely in the course of a week or ten days *Ocular paralysis* may occur in the fourth to sixth week of the disease The two commonest types are *oculomotor* affecting the external rectus of one or both sides thus resulting in a convergent squint and *ciliary* in which the power of accommodation is weakened or lost Spontaneous recovery in the course of a week is the general rule Rarer forms of cranial nerve palsies are *facial pharyngeal* and *laryngeal* paralysis The prognosis in these forms is good unless there is concomitant involvement of the respiratory muscles

Paralysis of the peripheral nerves appears somewhat later than do the cranial nerve palsies the usual time of occurrence for the former is between the fifth and eighth week of the disease The commonest form is a polyneuritis of the lower extremities as evidenced by weakness or paralysis of certain muscle groups Total loss of function is rare and sensation is unimpaired Complete recovery over a period of a few weeks is the general rule Less commonly the upper extremities the neck and the trunk may be involved Again in general the prognosis is good if however the intercostal muscles are involved there is danger of serious respiratory embarrassment particularly in the presence of diaphragmatic weakness or paralysis

It must be emphasized that polyneuritis of diphtheritic origin may occur in the absence of faucial manifestations of the disease During World War II it represented the most important sequela of so-called "wound diphtheria"

Treatment The prompt administration of diphtheria antitoxin in adequate amounts is the first and most important step Laboratory studies and clinical experience have demonstrated the importance of administering antitoxin as early as possible in the course of the disease Presumably the union between toxin and cell is a stable one which cannot be broken down by any practicable amount of antitoxin the role of the latter is confined therefore to neutralizing unbound toxin circulating in the blood stream and other body fluids thereby protecting the undamaged cells which have not come into intimate contact with the toxin as yet Antitoxin should be administered as soon as diphtheria is suspected on clinical grounds without waiting for confirmation from the laboratory Attainment of the early treatment of the actual case of diphtheria is well worth the price of administering antitoxin unnecessarily to an occasional individual In a severe case of diphtheria the prognosis depends largely upon how early an adequate amount of antitoxin can be administered

There is no agreement among clinicians as to the amount of antitoxin that should be administered A conservative scheme calls for 10 000 to 20 000 units for mild cases 25 000 to 50 000 units for moderate cases and 50 000 to 100 000 units for severe cases These figures are for the average adult but in actual practice age and weight are not often taken into account except among the very young The total dose required should be administered at one occasion if possible The route of administration may be intramuscular or intravenous The latter route has the advantage of speedier absorption but in theory gives a greater risk of an overwhelming anaphylactic reaction In general the intramuscular route is preferred for doses up to 20 000 units and the intravenous route for amounts above this The subcutaneous route should not be used since absorption is relatively slow

As diphtheria antitoxin is a foreign protein (horse serum) precautions should be observed against the occurrence of hypersensitivity reactions (*i e* anaphylaxis) These are (1) inquiry of the patient or of his family concerning a history of sensitivity to horses (or horse products such as dander etc) or of previous exposure to horse serum and (2) performance of ophthalmic and intradermal sensitivity tests In both tests a 1 10 dilution of antitoxin in saline is used In the first method one drop of this dilution is dropped into the conjunctival sac and the eye is observed for the development of redness during the next thirty minutes In the second method 0 1 ml of the 1 10 dilution is injected intracutaneously in the forearm and the area is observed for the development of erythema

wheals and similar reactions for the next half hour If a positive reaction is obtained by either method it is *prima facie* evidence of sensitivity to the horse serum and hence antitoxin should be administered with caution Desensitization is carried out by giving small doses of highly diluted antitoxin by the subcutaneous route at first and then gradually working up to the intramuscular and intravenous routes until the full dose has been given Desensitization may be a tedious and nerve racking task but as antitoxin is the only specific therapeutic weapon available it is a process which must be carried out in cases in which sensitivity exists Epinephrine must be at hand before antitoxin is administered by any route

Since it has been shown that the administration of certain antimicrobial drugs (notably penicillin and erythromycin) helps to eliminate the causative organisms from the nasopharynx there has been an understandable tendency toward the routine use of one or more of these drugs in the treatment of *all* cases of diphtheria Although diphtheria bacilli are susceptible to the action of these drugs *in vitro* the latter have no neutralizing effect upon the toxin thus they cannot be substituted for antitoxin They find their greatest usefulness in the prevention of secondary infections and in the treatment of chronic carriers

General Management Complete bed rest is the first requirement The period over which this should be maintained depends upon the degree of toxicity and the presence or absence of cardiac complications In any event the return to activity should be gradual and guided by the careful observations of the physician Local therapy of the throat is rarely needed in the absence of secondary infection although hot saline irrigations may be comforting Dehydration should be treated with parenteral fluids containing dextrose Careful watch must be kept for signs of developing cardiac or neurological complications With these complications adequate rest is also the main feature of therapy Digitalis appears to be without benefit in the treatment of cardiac complications The patient should be kept isolated until two successive daily cultures are negative for the presence of virulent diphtheria bacilli

Prevention *Active immunization* represents the basic means at hand with which to control the occurrence of clinical diphtheria Of the various preparations available fluid toxoid and alum precipitated toxoid are the most widely used in the United States Both preparations consist of a filtrate of a broth culture of diphtheria bacilli (*i e* diphtheria toxin) which has been treated with 0 3 to 0 5 per cent formalin at a temperature of 37 C until toxicity has disappeared The resulting fluid toxoid is given in a primary course consisting of three injections (0 5 ml 1 0 ml 1 0 ml) at weekly intervals If suitable amounts of alum are added to the fluid toxoid a precipitate forms This alum precipitated toxoid may be resuspended giving a relatively purified immunizing preparation with a slightly superior antigenic potency because of a local stimulating effect of the alum on the tissues A primary course consists of two 1 ml injections spaced a month apart Against the obvious advantage of the alum precipitated toxoid must be weighed the fact that the greater sensitizing ability of this preparation may lead to unpleasant reactions upon subsequent reinjection In addition a sterile abscess occasionally develops at the inoculation site as a result of the irritating action of the alum Both fluid and alum precipitated toxoid are excellent immunizing agents at least 85 per cent of persons receiving a primary course may be expected to become Schick negative

The primary course of active immunization should be administered within the first year of life preferably at about the third month It may be combined with immunizations against tetanus and pertussis One stimulating dose should be administered two years later and another at the time the child enters school In susceptible older children or adults the possibility of a sensitivity reaction to the toxoid should be guarded against by the prior administration of 0 1 ml of a 1 10 dilution of fluid toxoid intradermally (the *Moloney test*) The development of a local reaction (best described as a severe pseudo Schick reaction) is warning that toxoid must be administered cautiously in multiple small suitably diluted doses These reactions fortunately almost unknown before adolescence represent the great problem in immunizing adult population groups Presumably they represent some degree of immunity and the mere carrying out of a Moloney test in a person giving a positive reaction may serve as an adequate antigenic booster

Passive immunization is possible since the administration of relatively small amounts of antitoxin (1000 units) will confer protection for a period of two to three weeks Because of the danger of inducing sensitization or of eliciting anaphylactic shock in a

person already sensitized to the foreign protein its use should be limited to immunization of persons peculiarly at risk of infection as for example nonimmunized children heavily exposed to virulent diphtheria bacilli Inasmuch as the protection conferred by antitoxin is of such short duration active immunization with one of the toxoid preparations should be carried out at the same time

In the event of an outbreak of diphtheria in a closed community (such as a school) the exposed persons should be observed closely in order that antitoxin may be administered at the first sign of suspicious illness Routine throat cultures usually yield little information of practical value The exposed persons should be given Schick and Moloney tests and those found susceptible and not sensitive should be immunized promptly with one of the toxoid preparations Under special circumstances the administration of prophylactic antitoxin may be indicated

F S CHEEVER

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Clostridium Infections

General Considerations The clostridia that is the anaerobic gram positive spore bearing bacilli are so widely distributed in nature—in soil and garbage in dust of all kinds and in the intestinal tracts of most animals—that they are frequently found in pathological lesions Although as might be expected they are particularly common in open wounds where they may produce various severe infections these organisms can under suitable circumstances attack almost any tissue of the body Nevertheless their mere presence in a lesion is of little significance for the clostridia require special and delicately adjusted environmental conditions before they can produce manifestations of disease In other words and this cannot be too strongly emphasized the clostridial infections of man are *clinical* and not *bacteriological* entities

This fact has given rise to some difficulty in assessing the relationship of these organisms to disease but in a broad way the many and varied pathological conditions due to the clostridia may be divided into two main groups *neurotoxic* which includes botulism and tetanus and *histotoxic* in which various tissues of the body particularly the muscles are invaded and destroyed Although it is primarily the histotoxic infections of man with which this section is concerned it should be pointed out that simultaneous infections with both histotoxic and neurotoxic clostridia can occur Thus particularly in war time the association of gas gangrene and tetanus is not uncommon *Cl botulinum* has also been recovered from infected wounds and on at least three occasions has produced a fatal and clinically typical infection in this way Finally it should be mentioned that in addition to infection of traumatized tissues one species *Cl perfringens* has been implicated in the syndrome of acute gastrointestinal disease

HISTOTOXIC INFECTIONS

GAS GANGRENE

Of the many different species of clostridia only a small number are truly histotoxic and capable on their own of initiating severe and frequently fatal infections Of this limited group of organisms the most important are *Clostridium perfringens Cl novyi Cl septicum Cl histolyticum* and *Cl bifermentans (sordellii)*

Toxin Production All of these species of clostridia owe their pathogenic powers to the production of one or more potent exotoxins These exotoxins are among the most powerful poisons known and are (with one minor and unimportant exception) entirely species specific This point is of considerable practical importance in that the antitoxin prepared against *Cl perfringens* is quite useless in combating an infection with *Cl novyi* Moreover all the clostridia mentioned probably produce several different toxins *Cl perfringens* elaborates no less than twelve *Cl novyi* at least six and *Cl histolyticum* three and there can be little doubt that more toxins remain to be discov

ered However it is fortunate from a practical point of view that in any one species there appears to be but one single toxin of overriding importance in the genesis and progression of the disease and it is against this toxin that the appropriate antiserum is prepared It should be mentioned here that a classification of *Cl perfringens* and *Cl novyi* into subspecies has been made in recent years on the basis of the various toxins produced or the different combinations of the same toxins thus six types of *Cl perfringens* A B C D E and F and three types of *Cl novyi* A B and C are now recognized So far as human infections are concerned only *Cl perfringens* types A D and F and *Cl novyi* types A and B are of interest to us Finally it must be pointed out that certain of these toxins including some of great importance have been shown to be enzymes and that their specific substrates have been identified This of course is a discovery of the greatest importance not only for our understanding of clostridial infections but for our investigation of disease processes in general

Mechanism of Production of Gas Gangrene It has already been stated that clostridia require special environmental conditions within the host before they can produce their pathological effects—indeed before they can even grow Although it is known in a broad way what these essential factors are detailed knowledge of this complex problem is still meager The fundamental point to be borne in mind is that all these organisms are strictly anaerobic and will grow and produce their toxins only under conditions of markedly reduced oxygen tension In the animal body such conditions may be achieved by various means the prolonged application of a tourniquet the pressure of a tight plaster slight trauma the presence of necrotic tissue in a wound the occurrence of foreign bodies such as earth shell fragments or clothing and even necrotizing lesions due to aerobic organisms Any of these situations is sufficient to permit germination of clostridial spores the multiplication of the clostridia and the elaboration of toxins Once the toxins have been produced the process is relatively simple The toxin diffuses out into the surrounding tissues kills them and so permits the organisms themselves to spread into new areas of reduced oxidation reduction potential There the process is repeated and so the disease continues to spread gaining momentum and severity as it progresses

That is the process in broad outline of the details we are far less certain In the case of *Cl perfringens* the organism most studied it seems clear that the alpha toxin is the element of prime importance This has been shown to be a *lecithinase* which can readily kill tissue cells by attacking the lecithin present in the cell wall Diffusion through the entire infected area is aided by the production of a *collagenase* a *hyaluronidase* and a *fibrinolysin* each of which can break down certain of the binding elements in the tissues Although fully toxigenic strains of clostridia may be found multiplying in the depths of many wounds only when these organisms invade muscle tissue do they become really dangerous The reason for this anomaly is far from being understood though various hypotheses have been advanced in recent years Indeed we are as yet uncertain of the ultimate cause of death in gas gangrene

Destruction of muscle tissue should not in itself be fatal yet it may be safely said that every untreated patient with gas gangrene will surely die For this reason it has generally been assumed that death has been due to the toxins gaining access to the blood stream and then lodging in various ill defined vital centers There is little evidence of such a process and it has been suggested that the lesion is essentially a local one analogous to the crush syndrome and similar sterile destructive lesions of muscle Final proof of this thesis is lacking

Pathological and Clinical Features Pathogenic clostridia may be found in any traumatic lesion but so far as man is concerned three main types of infections may be discerned *simple contamination anaerobic cellulitis* and *anaerobic myositis* However these are not strictly circumscribed clinical entities they are rather the most obvious stages in a continuous infectious process

Little need be said of *simple contamination* for in the majority of wounds the presence of clostridia is quite unsuspected on clinical grounds In *anaerobic cellulitis* on the other hand the anaerobic bacteria find conditions more suited to their needs and proliferate more widely producing gas in the tissues both by a proteolytic and a saccharolytic process The muscles as the name indicates are not invaded The condition usually develops three to six days after injury is of gradual onset and is unaccompanied by any severe signs of systemic upset Pain is usually absent Indeed by far the most obvious clinical signs are the presence of gas foul odor and a thin *brownish seropurulent discharge*

In *anaerobic myositis* or true gas gan

grene the process is far more acute and severe The onset is usually sudden with an incubation period from as little as six hours up to three days after injury has been sustained The most important and usually first symptom is pain in the affected area rapidly increasing in severity This is accompanied by tachycardia tachypnea and a fall in blood pressure Some elevation of temperature usually is seen but the degree of fever is not related to gravity of the illness On early inspection the skin is pallid and may be tense and shiny because of underlying edema The wound exudes a brownish or blood tinged serous discharge with a foul odor At this stage there is often no evident crepitation since this may be masked by accumulating fluid in the tissues Actually the amount of gas produced is rarely so pronounced as the name of the disease would indicate As progression occurs the skin assumes a dusky or bronze appearance and finally if the patient survives long enough it becomes deeply discolored and exhibits vesicles filled with dark red liquid which tend to coalesce Herniation of muscle through wounds or incisions may result from increased pressure within the tissues In later stages of the disease prostration is a dominating feature often accompanied by a peculiar apathy or indifference on the part of the patient Stupor delirium or coma may occur

The abnormal changes in involved muscle can best be observed at operation These consist of swelling loss of contractility and alteration in color varying from pallor to a deep red mottling Bubbles of gas frequently can be expressed by manipulation

Uterine infections usually caused by *Cl perfringens* probably represent the most common form of gas gangrene encountered in civilian practice These infections ordinarily result from attempted criminal abortion but they may also follow prolonged labor or instrumental delivery The course is similar to that already described except that bacteremia and massive hemolysis are more frequent complications Intravascular hemolysis which occurs in many cases is generally associated with acute renal failure caused by a lower nephron type of nephrosis Although some writers have stated that hemolysis never happens without invasion of the blood stream by *Cl perfringens* the complete picture of shock anuria and hemolysis may be seen in the absence of demonstrable bacteremia whereas patients with positive blood cultures may show no evidence whatsoever of either renal damage or a hemolytic reaction The fatality rate in uterine infections continues to be high since many patients who survive the acute phase succumb later to the effects of renal insufficiency

Diagnosis Gas gangrene is a clinical and not a bacteriological entity and diagnosis rests primarily on the appraisal of clinical phenomena already described The most important of these are pain edema and the general condition of the patient It must be emphasized that other types of infection can cause the formation of gas in tissues so that its demonstration by roentgenography or the presence of crepitation does not specifically incriminate clostridia Bacteria of the genus Aerobacter or Escherichia may be responsible for gas production and indeed within certain limits it can be said that cases with the most obvious and extensive early signs of aerosis are among those less likely to have gas gangrene

Most observers agree that stained smears of the exudate from wounds or from the cervix when the uterus is implicated give important diagnostic information if they reveal typical gram positive bacilli in large numbers Roentgenographic examination also may be helpful in incipient cases involving the extremities by disclosing the presence of gas and its spread along fascial planes

Treatment As is prevention treatment is almost exclusively the province of the surgeon The operative procedures generally consist of multiple incision and fasciotomy for the drainage of fascial compartments and open amputation if necessary Among females with septic abortion curettage is usually performed in early cases and hysterectomy is not done unless there is clinical evidence of perforation of the uterus In advanced cases hysterectomy has been associated with a high operative mortality

Supportive measures are of great importance especially those designed to alleviate shock by the administration of blood plasma fluids and electrolytes so as to maintain blood volume and arterial pressure Careful attention to these details of the therapeutic program is essential particularly in patients with renal failure and anuria Antimicrobial drugs must be given penicillin is the agent of choice in doses of no less than 1 000 000 units every three hours in addition since mixed infections are frequent it is advisable to give one of the tetracyclines in a minimal dose of 0 5 gm every twelve hours preferably by the parenteral route The efficacy of polyvalent gas gangrene antitoxin is questionable

Nevertheless in severely ill patients the administration of 40 000 units of antitoxin intravenously every six hours is advocated provided that cutaneous tests for sensitivity to the serum have been done beforehand and are negative

Prevention Prophylaxis is almost entirely a surgical problem and rests upon the well established principles of prompt treatment after injury adequate removal of devital ized tissue and foreign bodies and proper supportive management Gas gangrene anti toxin is of no value in prevention nor should any reliance be placed on anti microbial drugs In the handling of surgical patients tourniquets should be used cau tiously and bandages or plaster casts must be applied carefully so as to avoid inter ference with the circulation Toxoids for active immunization are still in the experi mental stage

CLOSTRIDIAL GASTROENTERITIS

Quite apart from these traumatic infec tions it has recently been established that *Cl perfringens* may also be involved in various gastrointestinal diseases

The simplest of these is a mild gastro enteritis differing in no way from food poisoning due to other bacterial species An aberrant form of *Cl perfringens* type A has been implicated in this condition it has been isolated from the suspected foods from the stools of patients and in volun teers has produced a similiar clinical pic ture

A much more severe infection is *enteritis necroticans* in which there is an acute regional gangrene of the small intestine particularly of the jejunum This disease first appeared in Northwest Germany toward the end of World War II and by 1946 several hundred cases were known to have occurred in this area Essentially similar cases have since been reported both in England and the Americas There can be little doubt that the exciting agent is *Cl perfringens* type F This organism differs from the classic type A in producing rela tively little of the alpha toxin (the lecithin ase) but large amounts of the beta toxin The beta toxin it may be added is a hemolytic necrotizing and lethal factor known to be of importance in various enterotoxemic diseases of domestic animals Infection apparently occurs by the inges tion of contaminated food stuffs of which by far the commonest have been canned or preserved fish and meat The signs and symptoms of the disease are those of any similar acute lesion of the small intestine so that the specific diagnosis has as a rule been made only at operation or more com monly at autopsy The fatality rate is high and treatment has usually consisted of sup portive measures together with the oral administration of various sulfonamide prep arations Serum therapy appears to have been of little value but the data are in sufficient for a final evaluation Much the best results have been obtained by surgical resection of the affected areas of the gut but for technical reasons this is not always possible

Several reports of gastroenteritis ap parently caused by *Cl perfringens* type D have also been published but such cases are distinctly unusual This clostridial spe cies has long been known to be the cause of enterotoxemic disease in sheep It may also produce a similar disorder on rare occasions in man generally as a complication of *damage to the bowel from other causes* such as intestinal obstruction Epsilon toxin elaborated by the microorganism is believed to be an important factor in the pathogen esis of the enteritis

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NEUROTOXIC INFECTIONS

TETANUS

Definition Tetanus is a neuromuscular disorder often referred to colloquially as lockjaw which is caused by a specific exo toxin of the infectious agent *Clostridium tetani*

History The disease has been recognized as a clinical entity since antiquity especially as a sequel to wounds sustained in combat but definitive knowledge of its nature and of means for its preven tion and treatment was not acquired until the close of the nineteenth century Nicolaier in 1884 pro duced tetanus by injecting animals with samples of garden soil and described a bacillus resembling *Cl tetani* at the loci of inoculation However the micro organism was not isolated in pure culture until 1889 by Kitasato In 1890 von Behring and Kitasato published their classic report of successful immuni

zation by repeated small doses of toxin and the neutralization of toxin by specific antiserum this great discovery laid the foundation for all subsequent work on immunological methods of prophylaxis and treatment Evidence for the central action of tetanus toxin advanced by Marie and Morax in 1902 and by Meyer and Ransom in 1903 was subsequently challenged by Abel and his associates but recent studies by Wright Brooks and colleagues have fortified the earlier views Ramon was responsible for the introduction in 1925 of tetanus toxoid for active immunization and for procedures whereby toxoid and antitoxin may be standardized

Etiological Agent *Clostridium tetani* is a strict anaerobe and one of the few pathogenic microorganisms which may be identified with reasonable certainty on morphologic grounds alone This is owing to the fact that in sporulating forms the spore is located terminally thus giving a characteristic "drumstick" or squash racket appearance to the cell

The many studies on resistance of tetanus spores to heat and chemical agents have given varying results It may be concluded however that none of the antiseptic agents employed clinically can be relied on to devitalize spores nor is simple boiling an entirely safe procedure Autoclaving at 120° C for 15 minutes is the best method for sterilizing potentially contaminated instruments and equipment

Although ten distinct antigenic types of *Cl tetani* have been recognized by differences in their flagellar antigens all of them fortunately elaborate the same antigenic type of exotoxin which may be neutralized by a single antitoxin The toxin has been isolated in crystalline form and is a protein with molecular weight of approximately 67 000 Next to botulinum toxin it is the most powerful poison known each milligram of nitrogen corresponding to about 75 000 000 guinea pig M L D units In solution the toxin is unstable and converts spontaneously to toxoid apparently by molecular dimerization this conversion is accelerated and driven to completion by 0 4 per cent formalin

Epidemiology Although tetanus is relatively uncommon the responsible agent is widely found in nature its chief distribution being in the soil and in the gastrointestinal tract of man and a wide variety of animals In fact its occurrence elsewhere may be said generally to depend on contamination from either of these two sources There seems to be little doubt that a direct relationship exists between the extent to which soil is cultivated and its degree of contamination by tetanus spores The population density of man and animals as well as climatic conditions terrain and types of soil is also an important factor These points are exemplified by the fact that *Cl tetani* has rarely been recovered from virgin soil or from areas of wasteland while a high percentage of positive results has usually attended the investigation of samples from urban and agricultural communities

Studies of the carrier rate of *Cl tetani* in the intestinal tract of man have yielded widely divergent results but have served to show that rural inhabitants especially farm workers harbor the microorganism much more frequently than do city dwellers or persons of sedentary occupation These findings illustrate the epidemiological significance of sanitary conditions and of contact with horses and cattle

As might be expected from its natural habitat and general distribution *Cl tetani* has been frequently isolated from the surface of the human body and occasionally from the oral cavity It exists not uncommonly in house dust and has been recovered with disturbing ease from the floors of operating rooms where it probably was introduced by footwear Plaster of paris and surgical dusting powders have also been found to be contaminated

In spite of the ubiquity of the etiological agent the incidence of tetanus is for the most part remarkably low For example during the five year period ending in 1955 an average of approximately 500 cases were recorded annually in the United States although doubtless others were not reported This represents a considerable decline in incidence over the last two decades which probably reflects the shift of population toward cities the general improvement in medical and surgical care of injuries and the greater use of tetanus toxoid as part of the immunization program in childhood

A recent survey of tetanus in the United States for 1947–1955 showed that the incidence was highest in the South and that throughout the country the mortality rate among nonwhite persons was 5 to 6 times greater than in the white population It was also found that more deaths occurred in children less than one year of age than in any other age group These observations serve to emphasize the correlation of the disease with poor sanitation and inadequate medical services

Pathogenesis It is well known that tetanus almost always results from some sort of injury occasionally of the most trivial nature For instance in addition to tetanus

following war wounds highway accidents burns and other major types of trauma the disease has supervened after hypodermic injections smallpox vaccination the peck of a hen an insect bite and so on In occasional cases particularly among children it may be impossible to determine which of several minor injuries may have been responsible while in some patients no wound at all may be discovered

The all important feature of the initial event is that spores of *Cl tetani* must be deposited or exist already in tissues where the conditions are properly altered to suit its exacting metabolic requirements In general this means an area where the tissue has been devitalized and the oxidation reduction potential is properly poised to permit multiplication and toxigenesis The infection itself once started remains remarkably well localized at the original site since the invasive powers of the microorganism appear to be even feebler than those of *Corynebacterium diphtheriae* This fact incidentally is responsible for the former advocacy now outmoded of local excision or even amputation as a part of treatment

The disease proper is unquestionably caused by tetanus toxin but the mechanisms whereby it is absorbed and produces its effects are still largely unknown The early work of Marie and Morax and of Meyer and Ransom led to the theory that the toxin acted centrally in the nervous system rather than peripherally in the affected muscles and that it gained access to motor cells of the spinal cord by a centripetal spread via regional nerve trunks In cases of local tetanus it was assumed that the amount of toxin released was relatively small and that involvement of the cord was confined to the anterior horn cells mediating the regional reflex arcs It was also assumed that generalized tetanus represented a further spread of toxin by neural pathways in the cord itself to involve the motor areas more widely These concepts were challenged by Abel and his associates in a series of papers about 1935 in which experimental evidence was adduced that the toxin had a peripheral rather than a central action and was distributed by the blood stream rather than by nervous channels Since then additional support for both points of view has been brought forward from various sources but during the past few years the work of Wright Brooks and colleagues has convincingly shown the probable correctness of the first theory This work is too extensive to be described here and the reader is therefore referred to the original references

The mode of action of tetanus toxin is entirely unknown No substrate for the toxin has been found attempts to demonstrate anticholinesterase activity have given negative results and no effect on production of acetylcholine has been clearly shown Certain investigators have claimed that the toxin acts as an enzyme to release a hypothetical substance with strychnine like activity but this suggestion does not seem to deserve serious consideration

Morbid Anatomy Tetanus toxin fails to produce any recognizable pathological lesions in the tissues it affects nor do any specific changes occur at the site of infection by *Cl tetani* In certain cases fractures or muscle disruptions may occur as the result of tetanic spasms

Incubation Period The incubation period in tetanus ranges from about three days up to four weeks and in exceptional cases even longer It should be stressed that the severity of tetanus and hence its outcome are related to the period of incubation cases with onset less than one week after injury having in general a more fulminating course This fact should be borne in mind in anticipating the therapeutic management of patients

It should also be noted that the incubation period may sometimes be extremely protracted in the sense that infection may be regenerated from spores which have resided in tissues for months or even years A case is on record in which tetanus developed fourteen years after an original war injury and in another *Cl tetani* was recovered from a hysterectomy scar ten years following postoperative tetanus Numerous accounts of shorter periods of latent infection have appeared In traumatic surgery especially of war wounds reoperation at the site of earlier injury may reactivate dormant spores and care should be taken in all such cases to ensure adequate immunological prophylaxis beforehand

Clinical Manifestations Tetanus may occur in a localized form but more frequently the neuromuscular disturbance is generalized Local tetanus is seen chiefly in persons who develop symptoms despite the prophylactic administration of antitoxin and consists usually of persistent spasm in muscle groups near the site where the injury or wound was incurred The spasm may last in diminishing intensity for several weeks In rare cases of head injury a cephalic type of local tetanus has been described with

bizarre combinations of motor phenomena depending on the involvement of one or more cranial nerves

More typically the onset of tetanus begins with an increase in tone of various muscle groups often accompanied by restlessness irritability and difficulty in swallowing Spasm of the masseter muscles which interferes with opening the jaws (trismus) is the most common initial symptom and its recognition should always suggest the possibility of tetanus to the physician As the disease progresses stiffness and rigidity of the neck back abdomen and extremities become more pronounced and involvement of the facial muscles may cause a grotesque grinning expression classically referred to as *risus sardonicus* Tonic spasms usually ensue in which the teeth are tightly clenched the neck and back are arched (*opisthotonos*) the abdomen is taut and the extremities are rigidly extended These spasms can be precipitated by the very slightest stimuli such as noise a draft of cold air jarring of the patient s bed sudden illumination of the room and so on in severe cases they recur frequently and apparently develop spontaneously Although duration of the individual tetanic episodes is ordinarily quite short their persistence is sometimes long enough to interfere seriously with the mechanics of respiration thus leading to anoxia and cyanosis and even to sudden death However the cause of death is usually less readily apparent and is generally attributed to exhaustion Throughout the disease the sensorium remains clear and therefore unfortunately the patient may be altogether conscious of the severe pain which invariably accompanies each tetanic spasm As a rule there is some degree of fever with temperatures exceeding 103 F in occasional cases as well as elevation of the pulse and respiratory rates In patients who recover the signs and symptoms abate gradually after reaching their maximal intensity

It should be noted that many variations in symptomatology may be observed especially during onset of the disease By way of example the following initial manifestations have been described fever and chilliness headache stiffness of gait abdominal pain caused by muscular spasm difficulty in swallowing pain in the neck and back and biting of the tongue

Laboratory Findings There are no laboratory procedures which are helpful in the specific diagnosis or management of tetanus It has been suggested that electromyograms may aid in distinguishing the incipient disease from other disorders of neuromuscular function but from the practical standpoint they are of little value *The electroencephalogram shows no abnormal* changes even in fully developed cases thus indicating that the tetanic spasms are probably not cortical in origin

Bacteriological examination as a means of diagnosis not only is almost worthless but also may be dangerously misleading To isolate and accurately identify *Cl tetani* from a wound requires a minimum of two or three days and the microorganism cannot be recovered in a considerable proportion of cases Moreover although *Cl tetani* characteristically shows a terminal spore other terminally spored nonpathogenic anaerobes exist and may be present as incidental contaminants The direct microscopic examination of wound material from a suspected case of tetanus should therefore be undertaken only by an expert It is also important to point out that *Cl tetani* may be found among the bacterial flora of many surface infections without evidence of harm to the patient Consequently the chance discovery of *Cl tetani* on routine bacteriological study does not imply that the disease will necessarily follow

Differential Diagnosis Once tetanus has developed the diagnosis is usually regrettably simple but in the early stages it may be confused with several other disorders Local infections in the mouth may cause trismus especially when molar teeth are involved The diagnosis in such cases ordinarily is obvious but the possibility of tetanus originating from such foci should always be borne in mind Meningitis and encephalitis must also be differentiated at times although it is rarely possible for the alert physician to be seriously misled Trismus and muscular spasms occur in certain cases of encephalitis but characteristically the sensorium is clouded and other neurological signs exist In tetany the typical carpopedal spasm and absence of trismus should suffice to indicate the correct diagnosis The writer has observed a case of hysterical trismus following a lacerated wound in a person familiar with the natural history of tetanus

Prognosis In severe cases of generalized tetanus the outlook is grave and the mortality rate still approximates 50 per cent despite recent advances in therapy The unfavorable features to be stressed are a short incubation period and the rapid progression of symptoms after onset Patients with an incubation period exceeding ten days generally have a more benign course

and recover more frequently The disease also is apt to be less dangerous and severe in cases with no evident focus of infection and in persons who develop tetanus even though antitoxin has been given prophylactically

Treatment The treatment of tetanus varies widely according to the severity of the disease and the needs of the individual patient In general however therapy is designed to prevent further elaboration and absorption of toxin to control tetanic spasms and to provide supportive measures which will maintain respiration nutrition and fluid balance

The usual dose of antitoxin in adults is 200 000 units intravenously to be given only after a preliminary test to determine whether the patient is hypersensitive to horse serum If sensitivity is found to exist desensitization by the standard method will have to be carried out before the total dose of antitoxin is administered This amount of antitoxin should suffice to neutralize any preformed toxin which has not been absorbed as well as toxin liberated subsequently at the focus of infection *it will not affect toxin which already has been bound by nervous tissue* Local injections of antitoxin around the site of the wound or injury totaling 10 000 to 20 000 units may also be made although their efficacy is doubtful The intrathecal use of antitoxin is not recommended

Prompt surgical attention to the wounded or injured tissues is essential with special reference to careful debridement and the removal of foreign bodies However it is important not to undertake these procedures until antitoxin has been given in order that any toxin which is released by manipulation may be neutralized before it reaches the central nervous system Penicillin should also be given since it has been shown to eliminate *Cl tetani* rapidly in most but not all cases it also aids in controlling secondary wound infections and serves as a prophylactic agent against the otherwise common complication of pneumonia In most instances 300 000 to 400 000 units of a procaine penicillin preparation given every twelve hours will be adequate but in some cases larger amounts of penicillin and the additional use of other antimicrobial drugs with broader antibacterial spectrums may be required

Management of Muscular Spasm The management of muscular spasms is of vital importance and may be extremely difficult especially if the patient is suffering from severe generalized tetanus Treatment must be suited to the individual case but it is essential that continuous nursing care be provided and that a physician always be in immediate attendance Since therapy will not actually shorten the illness even though the course is greatly modified it must be *continued until muscular spasms and rigidity* have largely disappeared The common procedure is to combine the use of sedatives in heavy dosage with a muscle relaxant drug In order to administer these agents as well as to provide means for the intravenous administration of fluids electrolytes and nutrients it is advisable to place at least one indwelling needle near the wrist or ankle Two such needles are better for plugging may occur or it may be necessary to infuse immiscible drugs simultaneously *e g* *d* tubocurarine and thiopental sodium (Pentothal) Furthermore the dosage of two drugs used concurrently by this route can be more accurately controlled if they are given separately Sedation sufficient to cause loss of consciousness is usually required and thiopental sodium has generally been recommended as the drug of choice A 2 5 per cent solution is given by vein in doses which can only be determined by the response of the patient The objective is to cause relief of pain and spasm without dangerous depression of respiration Since treatment must often be continued for a number of days it is important to bear in mind that thiopental sodium has a cumulative action when administered repeatedly *In many cases* phenobarbital sodium and paraldehyde intramuscularly will be helpful adjuncts Tribromoethanol (Avertin) given rectally has been used but is not recommended Chloral hydrate also per rectum has been employed with satisfactory results in some patients but its irritative properties sharply limit the length of time it can be used by this route

For muscle relaxation a number of drugs are available but the literature is conflicting as regards their relative efficacy and the extent to which they should be employed *Curare* and curare like compounds have been most frequently used and probably represent the agents of choice if they are intelligently and carefully administered Their pharmacological effects are considered to result from a direct competition with acetylcholine which leads to a depression of excitatory action at the motor end plate Thus they differ markedly from drugs like mephenesin (Myanesin Tolserol) which causes central depression of reflex activity and from compounds producing

persistent end plate depolarization by an acetylcholine like effect e g succinylcholine D tubocurarine chloride may be used as a repository preparation in oil and wax containing 30 mg per ml The usual initial dose is 0 5 ml and later doses may be increased to 1 0 ml or more depending on the response of the patient The rapidity of absorption from this depot form of curare is usually slow but may vary considerably Consequently it may be found advisable to employ d tubocurarine chloride intravenously in an isotonic aqueous solution containing 3 mg per ml the initial dose generally being 3 mg for each 40 pounds of body weight Larger amounts may be required according to the needs of the patient but the drug must always be given under constant supervision with the knowledge that successive doses tend to show a cumulative type of effect The respiratory difficulty sometimes observed in patients receiving curare which results not from muscular paralysis but from bronchiolar spasm may be controlled by antihistaminic therapy Another compound similar to curare in its action is tri (diethylaminoethoxy) benzene triethyliodide (*Flaxedil*) which is claimed not to cause histamine like side reactions The initial intravenous dose of Flaxedil is approximately 1 mg per kg of body weight If the use of a curariform compound is not desired *mephenesin* may be given by vein in a 2 per cent solution This drug must be diluted in isotonic glucose or saline since it readily provokes phlebitis it is also a hemolytic agent and hemoglobinuria has been seen following its use Mephenesin is short acting and its dosage varies considerably from 1 to 6 gm being given over a one hour period Succinylcholine decamethonium and muscle relaxants of a similar type may also be employed but information concerning their use is insufficient to warrant recommending them as the drugs of choice

It has been reported that chlorpromazine may be used to advantage in combination with barbiturates and muscle relaxing agents and that it prolongs the sedative and anticonvulsant action of these drugs without causing circulatory or respiratory depression as well as relieving apprehension The best results apparently are obtained by intravenous administration

Cortisone is of dubious value in the treatment of tetanus

Tracheotomy In all cases it is essential that provision be made for the immediate treatment of respiratory arrest and for the maintenance of the patient s airway Cumulative experience has indicated more and more that early tracheotomy should be performed in severe cases in order to circumvent the problem created by laryngeal spasm and to permit the easy use of tracheal suction for removing secretions In addition tracheotomy will permit emergency oxygen therapy under intermittent positive pressure using the apparatus described by Harris and her associates In some cases a mechanical respirator will be necessary

Tetanic spasms are usually accompanied by profuse sweating and throughout the illness proper attention must be devoted to maintenance of the fluid and electrolyte balance and the nutrition of the patient In severe cases under heavy sedation a nasogastric tube may be inserted for feeding by this route but it should be borne in mind that the use of muscle relaxant drugs also may cause relaxation of the cardiac sphincter with a tendency to regurgitation Intravenous fluids containing glucose balanced electrolytes and amino acids should be used as in any situation in which prolonged parenteral alimentation is required and periodic chemical examinations of the blood should be carried out to aid in guiding this phase of therapy

Following recovery from tetanus the patient should always be actively immunized in order to prevent possible recurrence of infection from retained spores of *Cl tetani* There is no evidence that the disease itself confers subsequent immunity and second attacks have been described

Prevention The greatest single advance in the management of tetanus has been the development of methods for specific immunization against the toxin When such methods are properly employed the disease is almost entirely preventable It should be emphasized that *antimicrobial drugs are not effective preventive agents and must never be used alone in tetanus prophylaxis*

Temporary immunity may be passively transferred by the subcutaneous injection of tetanus antitoxin the usual dose being 1500 units regardless of the age or weight of the patient The antitoxin is actually standardized immune horse serum and can cause severe or even fatal anaphylactic reactions in persons previously sensitized or allergic to horse protein Whenever possible therefore a history of earlier immunizing procedures and allergic symptoms should be carefully sought and even when this is negative injection must be preceded by an intradermal test with 0 01 ml of the anti

serum Positive reactions to the test indicating hypersensitivity are of the immediate wheal and flare type occurring within less than fifteen minutes

The great value of antitoxin was first conclusively demonstrated during World War I and today it *is still the only reliable* means of preventing tetanus in persons who have not been actively immunized However it has many shortcomings most but not all of which result from the fact that it is a foreign protein In addition to the hazards of its use in patients who are already allergic a prophylactic dose of antitoxin may itself engender sensitivity to horse serum thus creating a difficult problem if readministration becomes necessary as well as a dangerous situation if other types of therapeutic horse antiserums should be given subsequently The writer has seen sudden anaphylactic death in a patient who incautiously was given gas gangrene antitoxin ten days following the prophylactic use of tetanus antitoxin Besides reactions of this sort antitoxin may cause either general or local serum disease of varying severity it is also responsible in rare instances for a peculiar form of peripheral neuritis predominantly involving the brachial plexus the mechanism of which although not well understood presumably has an immunological basis Passive immunization against tetanus also has other drawbacks the most notable being that antitoxin obviously cannot be given after every traumatic event while the physician has no way of predetermining when its use will be essential

Tetanus prophylaxis is more readily and more safely achieved by active immunization with toxoid which is available in two forms fluid and alum precipitated the latter type being more slowly absorbed and providing a longer antigenic stimulus Experiment has revealed in man that one injection of either toxoid causes little or no antitoxin to appear in the blood A second injection three to four weeks later usually results in the development of measurable antitoxin equal to or exceeding 0 1 standard unit per milliliter of serum which is generally accepted as the protective level A third injection after another three to six months stimulates an even more marked antibody response and thereafter adequate amounts of circulating antitoxin can be readily maintained by booster doses at intervals of three to five years At the time any injury is sustained that warrants tetanus prophylaxis the person who has completed the basic course of immunization and has continued to receive stimulating injections is merely given another dose of toxoid antitoxin is not administered Immunization in this manner was extraordinarily successful in preventing tetanus *among the armed forces of the United* States during World War II only 6 cases occurring in the Army and 2 in the Navy among personnel who had received the basic course of injections All these cases had short incubation periods and hence probably represented massive infections in addition it is possible that some of them had low serum titers of antitoxin since not all persons are good antibody formers

It is generally recommended that children or adults be immunized by giving three subcutaneous injections of 0 5 ml fluid toxoid at intervals of three to four weeks or two injections of 0 5 ml alum precipitated toxoid four to six weeks apart *Another injection of 0 5 ml of either toxoid* should be given six months to one year later Thereafter stimulating doses of 0 5 ml should be administered every four years In the event that prophylaxis becomes desirable a stimulating injection of 0 5 ml of *fluid* toxoid is given since this induces a more rapid rise in antitoxin than does alum precipitated toxoid If a previously immunized patient has not received toxoid for more than five years it is advisable to give both antitoxin 1500 units and fluid toxoid 0 5 ml Separate syringes must be used since mixture in the same syringe will result in partial or complete neutralization There is experimental evidence that the combined use of antitoxin and toxoid causes an initial sharp rise in the blood level of antitoxin provided by the passively transferred antibody which is overlapped by a secondary sustained elevation resulting from the antigenic stimulus of the toxoid In patients who are seriously injured with shock compound fractures or large massively contaminated wounds some authorities advocate that both antitoxin and toxoid be used regardless of the status of antecedent immunization

Proper surgical care is also essential in the prevention of tetanus In all types of trauma whether suffered in military or civilian life the well known principles of prompt treatment adequate débridement of wounds and the control of shock and secondary infection are of paramount importance

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Salmonella Infections

TYPHOID FEVER

Definition Typhoid fever is an acute illness lasting several weeks caused by *Salmonella typhosa* and characterized by sustained fever with headache and apathy cough splenomegaly a sparse maculopapular eruption and leukopenia

Etiology *Salmonella typhosa* is a motile gram negative bacillus which grows readily on simple infusion media Formerly called *Eberthella typhosa* it is now classified in the Salmonella group by most authorities because of similarities in biochemical properties antigenicity and pathogenicity Unlike most salmonellas it fails to produce gas during fermentation of sugars Final identification is made by agglutination with specific serum

The principal antigenic components of the typhoid bacillus are the flagellar or H antigen which is heat labile and the O or somatic antigen which is heat stable Virulent forms have another antigen located on the surface of the cell called the Vi antigen

At least twenty strains of S *typhosa* have been differentiated on the basis of susceptibility to lysis by bacteriophages This procedure has been helpful in studies of the epidemiology of typhoid but is not useful in clinical practice since there is no significant variation in the disease produced by different strains

Epidemiology *Salmonella typhosa* is a parasite of man and does not cause disease of other animals in nature The organisms are excreted in the urine and feces by patients with typhoid fever usually disappearing from the urine during the acute illness but sometimes persisting in the stools during convalescence Occasional patients become permanent *carriers* continuing to excrete bacilli in the stools for years after recovery from the disease Urinary carriers are rare except when there is coexistent disease of the urinary tract for example patients with schistosomiasis become urinary typhoid carriers rather commonly The bacilli do not multiply significantly outside the human body but may survive for weeks or months under natural conditions The danger from excreta of typhoid patients is well recognized and simple precautions are *effective in preventing infection of other* persons Much more difficult to control is spread of the disease by apparently healthy carriers who are responsible for its perpetuation

Infection of man invariably occurs by ingestion of fecally contaminated material Direct contamination of uncooked foods such as salads and raw milk by the soiled hands of a carrier has been the cause of many outbreaks while epidemics have occurred from sewage contamination of water or shellfish Flies may transmit the bacilli from feces to food Modern municipal methods of water supply and sewage disposal together with pasteurization of milk have almost eliminated large epidemics of typhoid fever As a result of these measures supplemented by improved sanitation in rural areas and active immunization the prevalence of typhoid fever has declined greatly in the United States since 1900 Although formerly occurring in huge summer epidemics the disease is now seen sporadically throughout the year Cases appear singly or in small groups and most of them are traceable to contamination of food by typhoid carriers

Pathogenesis Typhoid bacilli enter the body through the mouth It has been suggested that the organisms may lodge in the tonsils or pharynx and invade the interior of the body from there It seems more probable however that they pass through the stomach into the small intestine penetrate the lymphoid tissue in its wall and are transported to the mesenteric lymph nodes Multiplying in these locations the organisms then pass probably via the thoracic duct into the blood stream where they can regularly be demonstrated in cultures taken during the first week or ten days of illness The bacilli localize in lymph nodes spleen lungs bone marrow and liver Since bile is a good culture medium for S typhosa luxuriant growth takes place in the biliary tract this provides a continuous discharge of organisms into the small intestine and

contributes to the heavy involvement of the Peyer s patches which occurs during the second and third weeks of the disease The infection of the biliary tract also accounts for the positive stool cultures usually found at this stage Cultural studies on persons who die during the second or third week of typhoid fever have shown that the greatest concentration of the bacilli is in the biliary tract and duodenum with progressive dim inution in the number of organisms in the remainder of the small bowel and the colon

Antibodies for the typhoid bacillus gen erally appear in the blood during the second week of the disease and at about the same time bacteremia usually ceases There is no slackening however in the clinical mani festations The role played by antibodies in recovery is uncertain as is the reason for gradual regression of the infection There is some evidence however that typhoid bacilli can grow within cells particularly in plasma cells where they may be protected until the death of the sheltering host cells exposes them to the combined assault of antibodies and phagocytes Such a process might explain the slow defervescence of the disease

Second attacks of typhoid fever have been observed but as a general rule one attack confers lifelong immunity

Morbid Anatomy In nearly all tissues of the body there is proliferation of large mononuclear cells derived from reticulo endothelial tissue Lymphoid hyperplasia is notable everywhere but especially in the Peyer s patches of the ileum the mesenteric lymph nodes and the spleen The Peyer s patches may undergo necrosis leading to intestinal perforation or to hemorrhage The liver is usually enlarged and local areas of necrosis can be seen microscopi cally There may be a diffuse patchy pneu monitis

Symptoms The clinical manifestations of typhoid fever are subject to great variation in character and intensity The disease may take the form of a mild illness lasting only a week or two or it may last six to eight weeks Occasionally it is a fulminating proc ess which overwhelms the patient within a period of ten days The description to follow will pertain to cases of average severity lasting four to five weeks

The incubation period is ten to twelve days Abrupt onset is unusual more often there is gradual development of malaise headache and feverishness causing the pa tient to take to his bed about the third or fourth day The *fever* is remittent in type tending to be higher each day During the first ten days *headache* is likely to be the most prominent symptom accompanied by *general malaise* and a nonproductive *cough* *Anorexia* is the rule occasionally with *nausea* and *vomiting* *Constipation* is com mon during the first two weeks of illness and there is often generalized abdominal discomfort and distention *Epistaxis* is an early symptom in about one fifth of all cases By the third week the fever is gen erally high varying from 102° to 104° or 105° F each day There are periods of profuse sweats and occasional chills asso ciated with the temperature variations Ad ministration of an antipyretic drug is likely to result in a precipitous fall in tempera ture followed in a few hours by a chill and rapid return to the previous level There may be *delirium* at the peaks of fever The sensorium is dulled the patient often has a blank staring expression and may pick aimlessly at the bedclothes At this stage *diarrhea* may supervene and several watery grayish or greenish stools may be passed each day

Once the fever reaches a plateau it is sustained for a week or two then gradually begins to lessen Each day the remission is greater and the elevation a little less nor mal temperature being attained after about thirty days of illness

Physical Signs Physical findings vary ac cording to the stage of the disease In the first week aside from feverishness and per haps slight abdominal distention there are no helpful physical signs During the second week the *spleen* becomes palpable in about three fourths of all cases It is soft not greatly enlarged and may not be felt if palpation is carried out too firmly The *rash* appears during the second and third week It can be seen in about 90 per cent of white patients but is difficult to detect in the Negro It consists of crops of round slightly elevated *rose spots* 2 to 3 mm in di ameter which blanch under tension and persist two to five days The lesions are seldom numerous often less than a dozen can be seen at a time They are found prin cipally on the trunk especially on the upper abdomen and lower chest rarely they are found on the face and extremities Exam ination of the lungs may reveal scattered *moist rales* evidence of the bronchitis which is commonly present in typhoid fever Dur ing the first two weeks of illness the *pulse rate* may be comparatively slow in relation to the fever *e g* 85 per minute at a tem perature of 104 F but subsequently the pulse rate is usually proportional to the fever At the height of the illness *abdominal*

distention may be severe and there may be moderate *generalized abdominal tenderness* most pronounced on the right side All these signs subside as the fever diminishes and by the time the temperature has returned to normal the rash splenomegaly abdominal distention and bronchitis have usually also disappeared Convalescence is slow the patient is seldom able to resume former activity within a month after the fever subsides

Older descriptions of typhoid fever based upon the clinical picture seen around 1900 stressed the remarkable wasting which occurred as well as changes in the mouth and tongue sordes on the lips and teeth and parotitis With good nursing care administration of adequate fluids and nutriment these developments are now rarely encountered and will not be described in detail

Laboratory Findings During the course of the illness a normochromic *anemia* develops This may be aggravated by extensive bleeding into the bowel As a rule the *leukocyte count* is normal during the first two weeks of illness in the third and fourth weeks there is usually a neutrophilic *leukopenia* the total count ranging from 3000 to 6000 cells per cu mm *Albuminuria* of moderate degree is common when the fever is high The *feces* usually give a positive reaction for *occult blood* during the third and fourth weeks of the illness and sometimes they contain gross blood

Isolation of S typhosa from the Blood It is possible to isolate *S typhosa* from the blood in nearly all cases during the first week of illness but with diminishing frequency thereafter Blood culture is rarely positive after the third or fourth week unless the patient remains acutely febrile The organisms can often be cultivated from *bone marrow* however until the fourth or fifth week of illness Typhoid bacilli do not appear in the feces until the second or third week but by the fourth week *stool culture* is positive in approximately 85 per cent of cases The frequency of positive cultures declines rapidly thereafter and by the sixth or seventh week is less than 5 per cent In approximately 2 to 3 per cent of cases the organisms continue to be excreted in the feces long after clinical recovery *i e* the patient becomes a typhoid carrier This state may continue for as long as twenty or thirty years or may cease spontaneously at any time The *urine culture* reveals *S typhosa* during the third or fourth week in about 25 per cent of cases but persistent excretion of the bacilli is rare

Serological Tests Demonstration of development of H and O agglutinins (Widal reaction) during the course of an illness is strong evidence in support of the diagnosis of typhoid However two sources of misinterpretation should be recognized Persons inoculated with *typhoid vaccine* within the previous six to twelve months may have agglutinins Moreover persons who have previously had the disease or been vaccinated may exhibit an *anamnestic reaction* with reappearance of typhoid antibodies during some other febrile illness especially typhus fever or brucellosis Recent vaccination can usually be ascertained from the history The anamnestic response is characterized by early rise and fall in titer and by the fact that serological reactions for the responsible disease rise to even higher titers and persist longer than the typhoid antibodies It is useful to test for both O and H antibodies in the Widal reaction since infections with serologically related salmonella organisms may serve as antigenic stimulus for one or the other of these The H titer usually is higher than the O No arbitrary level can be given as diagnostic occasional patients never have antibody titers higher than 1 40 or 1 80 Demonstration of a rising titer is more significant than any single level although titers of 1 160 or greater especially for antibodies to the O antigen are strongly suggestive of active infection Tests for Vi antibodies are technically more difficult but a positive result is especially significant because typhoid vaccination does not usually cause development of Vi antibodies

Complications The most frequent serious complication is *hemorrhage* from the small bowel which results from erosion of blood vessels in the ulcerated Peyer s patches As already noted bleeding sufficient to give a positive test for occult blood in the feces occurs in nearly every case of typhoid fever during the third and fourth week Gross blood is present in 10 to 20 per cent of all cases Profuse bleeding is sometimes fatal Serious blood loss is evidenced by pallor shortness of breath tachycardia and fall in blood pressure In some instances there is also an abrupt fall in body temperature *Perforation* of the intestine is less frequent (about 2 per cent of cases) but is an even more serious complication often resulting in death Gross intestinal hemorrhage sometimes precedes perforation The clinical signs of perforation are often obscured by pre-existing abdominal distention pain and tenderness Usually however sudden intensification of pain occurs in the right lower abdomen with localized tenderness

and diminished or absent peristalsis Free air within the peritoneal cavity may be demonstrable on a roentgenogram The pulse rate often increases and a rise in leukocyte count is a helpful diagnostic sign *Pneumonia* may occur as an extension of the bronchitis which usually accompanies typhoid fever but occasionally it is caused by pneumococcus or some other microorganism *Cholecystitis* occurs in 2 to 3 per cent of patients and is characterized by pain and tenderness in the right upper quadrant Cholelithiasis may develop as a late sequel *Periostitis* occasionally occurs during or after the febrile period It is usually situated near the end of a long bone or in one of the vertebrae The lesion tends to flare up and subside at irregular intervals over long periods of time Typhoid *pyonephrosis* has been described *Thrombophlebitis* is uncommon *Meningitis* is rare *Arthritis* is also a rare complication the large joints being the ones affected *Abortion* or *premature delivery* almost always occurs in pregnant women

Relapse Relapse occurs during convalescence in about 10 per cent of cases This may amount to only a few days of fever or there may be a reappearance of all manifestations including bacteremia and "rose spots The course is usually short however and the clinical illness milder than the initial attack

Diagnosis *During the first week of illness* the diagnosis can be established by blood culture The appearance of rose spots and enlarged spleen during the second week is suggestive and at this time a rising titer of antibodies is usually demonstrable During the third and fourth weeks the causative organisms can nearly always be isolated from the feces Culture of bone marrow may be resorted to at any time during the first four or five weeks

Differential Diagnosis Because of the insidious onset with cough typhoid fever can be confused with *primary atypical pneumonia* Demonstration of pulmonary consolidation within the first week and development of cold agglutinins point to the correct diagnosis *Murine typhus fever* may be difficult to distinguish from typhoid Typhus fever is more likely to have a sudden onset with chills and a more profuse skin eruption Laboratory tests include a positive Weil Felix reaction and positive complement fixation reaction with typhus rickettsiae Clinical improvement with tetracycline would favor typhus fever In *tularemia* there may be a history of handling wild rodents or of tick bite and an ulcer with regional lymphadenopathy may be found Clinical improvement with streptomycin or tetracycline would suggest this diagnosis and development of agglutinins for *Pasteurella tularensis* would confirm it In *Rocky Mountain spotted fever* the onset is abrupt there may be a leukocytosis and the hemorrhagic eruption is usually heaviest on the wrists and ankles The Weil Felix reaction and complement fixation test are positive after ten days This illness also responds dramatically to therapy with one of the tetracyclines *Pulmonary tuberculosis* can usually be differentiated by roentgenographic studies but the presence of *miliary tuberculosis* is more difficult to exclude since lesions are not always demonstrable on the roentgenogram In such instances the diagnosis may be established by the appearance of choroidal tubercles the finding of tubercles in sternal marrow or the development of meningitis *Hodgkin s disease* localized chiefly in the abdomen may resemble typhoid fever but can be differentiated by negative bacteriological and serological tests for typhoid and eventual development of characteristic lesions in the mediastinal or superficial lymph nodes *Brucellosis* may be clinically similar but in cases which resemble typhoid antibodies against brucella or the microorganisms themselves should be demonstrable in the blood *Malaria* may have an onset similar *to that of typhoid but the typical relapsing* course usually becomes established after a few days and the plasmodia can be demonstrated in the blood smear The *paratyphoid fevers* simulate typhoid fever in all respects but are usually milder They can be differentiated only by serological and bacteriological methods

Prognosis Before the introduction of chloramphenicol the over all case fatality rate of typhoid fever was 8 to 10 per cent The prognosis is especially grave in cases with profuse hemorrhage or perforation It appears probable that with chloramphenicol therapy the fatality rate in typhoid fever can be reduced to less than 1 or 2 per cent

Treatment Attendants should be immunized against the disease They should wear gowns and should wash their hands with soap and water after contact with the patient or anything he may have touched Eating utensils should be boiled Bedding towels and so forth should be boiled The stools and urine can safely be disposed of in municipal sewage systems

Until 1948 there was no specific treatment for typhoid fever and patients with the disease had to go through a prolonged

severe febrile illness Careful nursing various supportive measures and maintenance of fluid balance and nutrition were of utmost importance With the introduction of chloramphenicol the situation has been altered This drug terminates the febrile period so quickly that the relative importance of nursing and general supportive measures has lessened

It is advisable to administer 2 or 3 gm of chloramphenicol daily during the first few days until the temperature is normal Thereafter a total daily dose of 1 0 to 1 5 gm is apparently adequate The daily dose can be divided into two or four parts and given at twelve or six hour intervals The pattern of response is remarkably uniform During the first two days there is little or no apparent change in the clinical condition fever continues and the symptoms are not modified Blood cultures reveal however that the bacteremia terminates within the first few hours after starting treatment During the third day dramatic improvement usually takes place The temperature subsides the symptoms abate the appetite improves and the patient enters the convalescent stage

It has been shown that an even more dramatic clinical improvement can be obtained by giving an adrenal corticosteroid as an adjunct to chloramphenicol therapy Cortisone in a dose of 200 mg daily for four or five days causes a rapid defervescence and lessening of the symptoms It can be discontinued at the time chloramphenicol would be expected to have the infection controlled So far as has been determined this use of cortisone has not been harmful to the patient

Relapses have been encountered in patients treated with chloramphenicol for only seven to ten days but resumption of the chemotherapy brings about rapid improvement Relapses can probably be prevented by continuing drug administration (in a dose of 1 gm daily) for three to four weeks Complications such as hemorrhage or perforation of the bowel may also occur even though the patient is afebrile and otherwise asymptomatic after chloramphenicol treatment and indicate the need for prolonged rest and careful observation Probably these complications can be reduced to a minimum by continuing chloramphenicol therapy for three to four weeks in all cases

Should a large hemorrhage occur blood transfusions are indicated The treatment recommended for perforation of the bowel formerly was surgical drainage but conservative treatment with tetracycline and chloramphenicol is now probably preferable

Treatment of Carriers Persons known to be carriers should not be permitted to work as food handlers The members of their households should be immunized against the disease Chloramphenicol is not effective in eliminating the carrier state Cholecystectomy will eradicate the carrier state in about 90 per cent of cases Before resorting to surgery however a trial of penicillin therapy in large doses should be given *i e* 10 000 000 units daily for 10 days This occasionally succeeds in terminating the carrier state

Prophylaxis Immunization against typhoid fever is practicable and reasonably satisfactory The vaccine usually used contains 1 billion heat killed organisms per ml In some parts of the world paratyphoid A or B bacilli are also included A course of immunization usually consists of three subcutaneous injections given at weekly intervals the individual doses being 0 5 1 0 and 1 0 ml The injection often causes some local soreness and there may be fever during the succeeding six to twelve hours The vaccine can be inoculated intracutaneously in doses of 0 1 ml This method reduces the likelihood of systemic reaction but the local pain and tenderness are as uncomfortable as with subcutaneous injection of the larger quantities Except with massive exposure the immunity conferred is reasonably satisfactory for six to twelve months and in many persons for considerably longer periods of time

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SALMONELLOSIS OTHER THAN TYPHOID FEVER

Definition Salmonella infections are a group of acute illnesses caused by the numerous members of the genus *Salmonella* The clinical picture may cover a spectrum ranging from severe enteric fever closely resembling typhoid to mild gastroenteritis

History The typhoid bacillus observed in tissue sections by Eberth in 1880 and isolated by Gaffky in

1884 was the first of a series of related organisms found to produce enteric infection in man *Salmonella enteritidis* was isolated by Gaertner in 1888 and *S typhimurium* shortly thereafter both from cases resulting from the ingestion of infected meat *S schottmuelleri* was obtained by Gwyn from the blood of a patient with paratyphoid fever in 1898 *S paratyphi* from contaminated water by Paladino-Blandino in 1903 and *S hirschfeldii* by Hirschfeld from cases of paratyphoid in Mesopotamia during the First World War among troops who had been immunized with TAB vaccine *Salmonella cholerae suis* isolated in 1885 by Salmon and Smith from swine and from cases of enteric fever in man by Longcope in 1902 was originally thought to be the cause of hog cholera but subsequent work has shown that it is only a frequent secondary invader in a disease caused by a virus The work of a large number of medical and veterinary bacteriologists has led to our present knowledge of this ubiquitous and important group of enteric organisms which now comprises over 150 species

Etiology The salmonellas are gram negative motile bacilli which may be distinguished from bacilli of the coli aerogenes group by their inability to ferment lactose and by their capacity for growth in the presence of certain compounds which inhibit the latter organisms These two characteristics form the basis for the methods using enrichment and differential media for their isolation from feces As a group the salmonellas do not produce indol or liquefy gelatin do not ferment sucrose lactose or salicin but produce acid and gas when grown in the presence of glucose mannitol and maltose with two exceptions—*S typhosa* and *S pullorum* which produce acid but no gas Identification of individual strains is usually made on the basis of biochemical activities and serological reactions in properly prepared antiserums

The modern serological classification of the salmonellas is based on studies of their antigenic structure by Kauffmann and White They may be divided into seven groups on the basis of their O (soma ic or heat stable) antigens and within these groups the individual types or species may be identified by their H (flagellar or heat labile) antigens Few laboratories are equipped for more than isolation of salmonellas and tentative identification of one of the common types Correct identification is important in tracing the epidemiology of these infections consequently many laboratories now forward the strains which they isolate to one of the Salmonella Centers for final identification *

Epidemiology The salmonellas are natural pathogens for a wide variety of animals and birds In general they may be divided into three classes (1) those species found only in man (2) those usually found in animals or birds but capable of causing disease in man and (3) those found only in animals or birds The first class is small including *S typhosa* *S paratyphosa* *S schottmuelleri* and *S hirschfeldii*—in other words the typhoid and paratyphoid A B and C bacilli All these organisms may cause enteric fever in general with somewhat diminishing frequency and severity as one moves down the list In contrast the frequency with which sepsis with focal complications or severe gastroenteritis characterizes the infection increases as one ascends the list The second class is the largest and is constantly growing The third is shrinking with more thorough bacteriological studies of sporadic cases and outbreaks of food poisoning Organisms of the second class rarely cause enteric fever but most often gastroenteritis or septicemia

Human infections with salmonellas are occasionally acquired by contact with infected animals but usually by ingestion of contaminated water or food Contamination of water and food may be caused by the excreta of animals such as rodents by flies by human beings who are sick or who are carriers or by infection in animals which are used as food Meat milk and eggs are the foods most frequently involved in transmission since the organisms may multiply in them before ingestion This rapid growth results in a large dose of bacteria and thus increases the likelihood of infection with *Salmonella* types of low pathogenicity for man

Important factors in spread are the relative resistance of the organisms to physical and chemical agents their ability to multiply outside the bodies of their hosts their widespread distribution in rodents domestic animals and fowls and the frequency of human carriers Approximately 3 per cent of typhoid patients become permanent carriers after the illness Although the percentage of permanent carriers is lower after paratyphoid infection a considerable number may carry the organisms for weeks or months and with the less pathogenic types inapparent infections occur frequently

Pathogenesis Much of our knowledge of the pathogenesis of enteric fever is derived from studies on typhoid fever by Goodpasture and Adams based on correlation of postmortem findings with experimental work in the chick embryo

The pathogenesis of infection with *Salmonella typhosa* is described in the im

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mediately preceding section on Typhoid Fever Presumably the general features of infection with other salmonellas are similar but permanent localization within the biliary system is much less common as is deep ulceration of the lymphoid tissue of the bowel Relapses and recrudescences appear to be due to reinvasion of the blood from secondary foci of infection

Immunity The degree to which an attack of infection with one *Salmonella* species confers protection against subsequent attacks with the homologous species or others of the same group is largely unknown Presumably the degree of immunity conferred by the disease will depend upon the intensity of the antigenic response evoked by the attack the interval before reexposure and the dose of infecting organisms This is borne out by experimental feeding of volunteers and by studies on actively immunized persons which indicate that the protection conferred by prophylactic vaccination is relative not absolute

Morbid Anatomy The pathological lesions found in these infections are not particularly specific Death seldom occurs except in severe enteric fever or in the septic cases The findings in the former are those of typhiod fever although the involvement of Peyer s patches is less prominent and ulceration much less frequent In the septicemic forms of infection intestinal lesions are usually absent and the findings are those of any acute generalized infection—acute splenic tumor focal necrosis of the liver cloudy swelling of the kidneys widespread petechial hemorrhages and occasional purulent foci in which the exudate consists of mixed polymorphonuclears lymphocytes plasma cells and macrophages

Pathological Physiology and Chemistry Like other gram negative organisms of the enteric groups the O or somatic antigens of the *Salmonella* are polysaccharide lipid protein complexes These antigens presumably are the heat stable endotoxins released as the result of autolysis and destruction of organisms in the body which give rise to many of the manifestations of the infection This statement is based on the result of clinical and experimental studies with purified endotoxins Their intravenous injection into human beings in minute amounts is followed after a latent period of thirty minutes to an hour by chill fever headache nausea malaise and leukopenia Recent studies by Wood and others suggest that the fever actually is caused by endogenous pyrogen released from leukocytes damaged by the action of endotoxin Antibodies against the O antigen develop after a week or two for the organisms from which the endotoxin was derived and the patient shows a steady increase in tolerance requiring constantly increasing doses to elicit the effect on each succeeding injection This phenomenon which is characteristic of the response to intravenous typhoid vaccine is not specific that is the tolerance is increased for endotoxins derived from any of the organisms of the enteric group and appears to be related to hyperplasia of the reticuloendothelial system

Incidence The incidence of salmonella infections bears a general relation to the degree of sanitation However in the United States despite the low incidence of typhoid fever in all but certain rural areas other salmonella infections occur with greater frequency The New York Salmonella Center collected 2916 cultures of *Salmonella* excluding *S typhosa* in the period from 1939 to 1945 comprising 53 types in 7 groups with the following distribution A (1 type) 0 7 per cent B (11 types) 32 6 per cent C_1 (11 types) 40 per cent C (7 types) 11 per cent D (5 types) 5 per cent E (8 types) 9 per cent F (10 types) 1 7 per cent The species most commonly isolated were the following the figures indicating the number of isolations B *S typhimurium* 795 *S schottmuelleri* 148 *S derby* 71 C_1 *S oranienburg* 709 *S choleraesuis* 144 *S montevideo* 134 C *S newport* 270 D *S panama* 95 *S enteritidis* 44 E *S anatum* 181

Symptoms Salmonellas cause three major syndromes in man *enteric fever septicemia* and *acute gastroenteritis* Although any of the pathogenic salmonellas may produce any of these three types of disease each syndrome tends to be associated with certain species The clinical pictures of these three syndromes are not completely distinct and many cases are seen in which the picture of one syndrome shades into the other

Enteric fever caused by *S paratyphosa S schottmuelleri* or *S hirschfeldii* and occasionally by other members of the group closely resembles typhoid fever but tends to be shorter in duration and milder and to have fewer complications although it can be a severe and serious disease The incubation period is shorter (one to ten days) rose spots are less frequently seen than in typhoid diarrhea is more common and there is considerably less ulceration of the small bowel so that hemorrhage and perforation although they may occur are

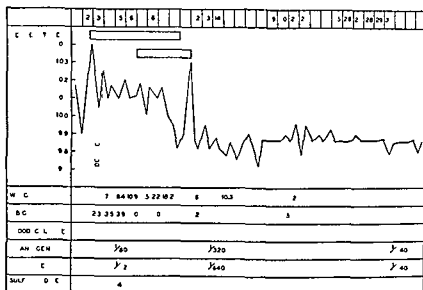


FIG 25 Clinical course of septic type of infection due to *S choleraesuis* in a 21 year old primiparous woman who had had a spontaneous delivery during the disease and who acquired pneumonia and arthritis of the sacroiliac joint as focal complications The baby appeared ill for the first week but recovered *S choleraesuis* was isolated from its stools on the twentieth day of life (Goulder Kingsland and Janeway New England J Med 226 127 1942)

less often observed Relapses are common and although the permanent carrier state occurs rarely as many as 20 per cent of patients may have positive stool cultures for several months after *S schottmuelleri* infection The differences between paratyphoid fever and typhoid fever are quantitative rather than qualitative and these two infections can be distinguished only by bacteriological methods

The *septicemic type of infection* is seen most often when *S choleraesuis* (*B suipestifer*) is the infecting organism This type of infection occurs sporadically and is usually seen in children or in adults debilitated by other diseases surgical operations or malnutrition The illness begins with an acute onset of high fever occasionally preceded by a chill In a few cases the onset is more gradual The bacteremia is uncomplicated by the development of focal lesions in about two thirds of these cases and the course is that of a typhoid like febrile disease with leukopenia and fever lasting one to three weeks Tachycardia is much more common than bradycardia and although cough coryza headache delirium stupor vomiting constipation and diarrhea all may occur as in typhoid fever they are much less frequent symptoms Intestinal hemorrhages and perforation have not been described

Focal complications are more frequently observed than in typhoid and paratyphoid fever Pulmonary lesions particularly bronchopneumonia have been noted in about one third of the cases Lobar pneumonia pleural effusion empyema and pericardial effusion have been observed In some cases the organisms have been isolated from the sputum or from the lung at autopsy

Bone and particularly joint lesions occur in about 20 per cent of cases according to Harvey The lesion is usually a pyarthrosis with organisms present in the greenish fluid which accumulates in the joint space and with involvement of the adjacent bone Any joint may be involved and the lesions frequently occur after the acute systemic infection has subsided

Purulent meningitis particularly in infants and children bacterial endocarditis superimposed on damaged valves pyelonephritis and abscesses in various part of the body have all been described as complications of *S choleraesuis* infection

The characteristic laboratory findings are a mild anemia which progresses during the disease and leukopenia which may be followed by the development of a leukocytosis when focal complications appear Bacteremia occurs in a high percentage of cases and persists throughout most of the febrile course The agglutination reaction becomes positive to a high titer in most cases Positive urine cultures are frequently obtained but positive stool cultures are rare

Acute gastroenteritis usually occurs in epidemics and may be caused by any of the salmonellas but *S typhimurium* *S oranienburg* and *S newport* are probably most often implicated in this country It results

from the ingestion of heavily contaminated food and begins abruptly with fever headache abdominal pains nausea vomiting and diarrhea after an incubation period of six to forty-eight hours In a few cases in any outbreak bacteremia may occur with high fever and chills or in children convulsions and drowsiness at onset cough pneumonitis splenomegaly muscle pains and weakness The course is brief usually lasting two to five days and the mortality low Generally there is leukopenia although leukocytosis often occurs particularly at the onset The clinical picture in such outbreaks depends to a considerable extent on the dose and pathogenicity of the infecting species In many instances when the dose is small or the infection due to organisms of low virulence for man such as *S pullorum* or *S anatum* gastroenteritis may be mild so that diarrhea cramps and slight fever are the only manifestations of infection In any outbreak a number of persons are found in whom positive stool cultures are obtained although they have no symptoms

Complications The complications of paratyphoid fever are those of typhoid fever but they occur somewhat less frequently—hemorrhage perforation urinary tract infections and in older patients circulatory collapse bronchopneumonia or thrombophlebitis with pulmonary embolism The septicemic forms of infection often due to organisms of the suipestifer (C_1) group may result in the development of purulent foci of infection particularly in the bones and joints but also in the meninges pleural cavity and elsewhere Gastroenteritis may result in dehydration and acidosis with serious results in the infant or debilitated elderly patient

Diagnosis The diagnosis of salmonella infection is a bacteriological one made by isolation of the organisms from blood feces urine or some local focus of infection It may be suspected from a rise in the titer of O agglutinins for any organism of the homologous group or of H agglutinins for the infecting or a serologically related strain The agglutination reaction is of more value in cases with blood stream invasion than in gastroenteritis Invasion of the blood occurs in the early stages of paratyphoid fever with later appearance of organisms in the stools while in most septicemic cases the organism may be isolated from the blood urine or from local foci of infection but rarely from the stool In gastroenteritis due to salmonella in contrast to bacillary dysentery organisms are more readily isolated from the stool later in the disease than at onset and frequently persist into convalescence

Although a definite diagnosis can be made only bacteriologically salmonella infection should be suspected in any case of unexplained fever particularly one in which leukopenia or gastrointestinal or joint symptoms occur In such cases differentiation from brucellosis or if rose spots are seen from one of the rickettsial diseases may be difficult Meningitis and pneumonia may be confused with salmonella infections since leukocytosis meningismus and cough frequently occur in salmonella infections with a rapid onset Salmonella gastroenteritis must be distinguished from epidemic nausea vomiting and diarrhea ("intestinal flu) which is probably a viral disease from poisoning from toxins elaborated by staphylococci streptococci or other organisms in the food before ingestion The first can be distinguished only on epidemiological grounds as a cold weather disease with a short incubation period apparently spread by droplet infection Food poisoning develops in a few hours after ingestion of the food Bacillary dysentery may be indistinguishable except bacteriologically and in all instances of gastroenteritis in which abdominal pain is severe differentiation of salmonella infection from acute appendicitis may be difficult particularly as diarrhea may occur when the appendix is retrocecal Elevation of the leukocyte count and localized pain and tenderness are the most helpful leads and suggest the need for a surgical approach Instances of appendicitis with rupture due to salmonella infection have been described

Prognosis The prognosis depends on the virulence of the infecting organism and the condition of the patient Septic infections due to *S choleraesuis* have a high case fatality rate (26 per cent in Seligmann s last series) This is nearly five times as high as the case fatality rate of 5 1 per cent for all salmonella infections in his 1107 civilian cases which should be contrasted with a rate of 0 12 per cent in 809 Army cases Age has an important bearing on mortality as in many other infections Most deaths occur in older people In children the infection though frequent is apt to be relatively benign except in very young infants

Treatment Acute gastroenteritis seldom requires more than symptomatic treatment—restriction of food intake to liquids and bland soft solids and if necessary repair of dehydration and provision of fluid

by the parenteral route In a few instances the use of antispasmodics such as tincture of belladonna or atropine or such time honored remedies as bismuth subcarbonate and paregoric may be necessary to control severe cramps

Enteric fever septicemia and severe gas troenteritis should be treated with chloramphenicol or a tetracycline in full doses (50 to 60 mg per kilogram in adults per 24 hours in four to six divided doses) continuing for seven to ten days after the patient has become afebrile The objective is symptomatic cure positive stool cultures frequently persist Unlike *S typhosa* the other salmonellas are by no means uniformly susceptible to chloramphenicol (or the tetracyclines) Consequently the physician may encounter a salmonella enteric fever with bacteremia that will remain relatively unaffected by chloramphenicol (or tetracycline) therapy In such circumstances if the patient is seriously ill it may be appropriate to administer an adrenocorticotropic hormone for a few days in addition to the drug therapy and to continue the latter alone thereafter

Prevention Sanitation is the key to control of these infections However the fact that many persons may be temporary carriers without symptoms of infection makes the problem of control difficult If meat and eggs are adequately cooked water and milk supplies controlled and fresh food is properly handled those infections which depend on a heavy dose of organisms should seldom occur Paratyphoid fever may occur as a result of a small infecting dose In view of the frequency of infections due to group C in this country it is surprising that the latter have not been included in the standard typhoid paratyphoid A and B vaccine However protection by vaccination is only relative and under conditions of heavy exposure infections may occur despite immunization

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Infections with the Coliform, Proteus and Pseudomonas Groups of Bacilli

Definition The various forms of infection caused by the gram negative aerobic bacilli normally present in the intestinal tract may be considered together under this heading

Bacteriology The coliform bacilli most of which are motile are differentiated from the salmonellas by their ability to ferment lactose There are two main types *Escherichia coli* (*B coli*) the predominant organism in the gastrointestinal tract of man and animals and *Aerobacter aerogenes* (*B lactis aerogenes*) usually capsulated which is also found in the bowel but derived primarily from vegetable sources Strains intermediate between the two classic representatives of the colon aerogenes group have been described while the *paracolon bacilli* which ferment lactose slowly occupy a position between them and the salmonellas The concept of a whole spectrum of organisms in the enteric group is further strengthened by the finding of some of the somatic antigens of the salmonellas in certain strains of coliform bacteria

Klebsiella pneumoniae (Friedlander s bacillus) is morphologically similar to *Aerobacter aerogenes* but is more virulent and may be isolated from the respiratory tract or from the bowel in a small percentage of normal people It occasionally produces gastroenteritis but is known chiefly as the cause of severe pulmonary infections *Alcaligenes faecalis* a motile organism found in normal stools may be confused with the enteric pathogens by its failure to ferment lactose in differential media but is identified by the lack of fermentation when grown in media containing the standard sugars This organism has occasionally been isolated in urinary tract infections and in cases of gastroenteritis bacteremia or meningitis in infancy

The *Proteus* bacilli are pleomorphic non lactose fermenting organisms characterized by active motility which gives rise to spreading growth on solid media These organisms although widely disseminated in decaying organic matter and feces are present in large numbers in stools only in abnormal circumstances *Proteus vulgaris* and *P morgani* the two species usually isolated from human infections are active urea splitters with the liberation of ammonia

Pseudomonas aeruginosa (*B pyocyaneus*) is a motile aerobic bacillus capable of producing two water soluble pigments—the bluish pyocyanin and fluorescein which is yellowish green and fluorescent Strains vary in their production of these pigments and some variants do not produce color This organism is occasionally recovered in small numbers from normal stools but more often is found on the skin It has been isolated from water sewage and air and improperly sterilized instruments solutions and surgical dressings

Etiology Recent work has implicated certain specific types of *E coli* as the cause of epidemic diarrhea in hospitalized infants and occasional mild gastrointestinal upsets in adults Since normally the coliform organisms are saprophytic inhabitants of the intestinal tract it is only under special conditions that they gain access to the body cavities or tissue spaces and initiate infection

In infancy resistance may be inadequate and these organisms may invade widely from foci in the respiratory or gastrointestinal tracts or in the newborn as a result of infection of the umbilical stump Elderly patients likewise may suffer from bacteremia due to these organisms usually as a result of some complicating factor such as carcinoma gallstones or renal calculi

In the abdominal cavity surgical infections arise secondary to obstruction perforation or interference with the blood supply of a hollow viscus Puerperal infections due to colon bacilli may occur as a consequence of poor obstetrical technique or difficult labor

Open wounds chronic infections of the middle ear and ulcerations such as bed sores in areas of poor circulation may become secondarily infected with gram negative bacilli particularly *Proteus* or *Ps aeruginosa* The latter organism may be introduced accidentally into the thecal space or the urinary passages as a result of instrumentation Indeed the development of meningitis following intraspinal anesthesia is almost invariably caused by *Ps aeruginosa*

Recently the intensive use of antimicrobial drugs has created a biological imbalance leading to elimination of susceptible strains of bacteria and their replacement by more resistant ones This phenomenon may occur not only in the individual patient during therapy but also in the hospital environment where the presence of a large number of patients under treatment with antimicrobials may lead to a marked increase in the population of drug resistant microorganisms in human carriers and in the dust Coliform organisms and *Staphylococcus aureus* seem particularly prone to develop resistance during the course of treatment while *Pseudomonas aeruginosa* which is usually resistant to the ordinary antimicrobial drugs has become an important cause of superinfection in treated patients

The most common disease produced by colon bacilli is urinary tract infection It often arises as a complication of diarrheal disease and is frequently seen in elderly patients with constipation Trauma to the urinary passages as from an inlying catheter stasis in the bladder or obstruction to the ureters predisposes to infection Urinary tract infections may be caused by any of the coliform bacilli in pure or mixed culture but the majority are due to *E coli* often in combination with the *Enterococcus* (*Streptococcus faecalis*) *Proteus* and *Pseudomonas aeruginosa* are usually encountered as secondary invaders in chronic urinary tract infections particularly after instrumentation and in chronic pulmonary infections

The incidence of urinary tract infection is considerably higher in women than men and diabetics are particularly subject to the disease In men some obvious mechanical difficulty such as neurological bladder prostatic hypertrophy urethral stricture or calculus can usually be found to account for the infection

Morbid Anatomy Acute infection with these organisms produces purulent inflammation In cases of bacteremia in infants there is a tendency to localization in the kidneys meninges lungs and serous cavities Contrary to earlier opinion the lesion in pyelitis has been found to involve the renal parenchyma as well as the pelvis and ureters so the term "pyelonephritis" has come into common use for this condition

The characteristic local lesions of the skin and gastrointestinal tract which occur in infections due to *Ps aeruginosa* are ulcerative or gangrenous On microscopic examination there is necrosis around a thrombosed small blood vessel with large numbers of bacilli in the surrounding tissue and relatively little reaction Leukopenia and hypoplasia of the bone marrow have been observed in some severe infections

Pathological Physiology and Chemistry All the gram negative enteric bacilli have potent endotoxins associated with their somatic antigens Consequently invasion of the blood stream by these organisms

gives rise to the same symptoms as those which follow the intravenous injection of typhoid vaccine chills fever headache nausea malaise and shock

Certain of these organisms particularly *Proteus* produce large amounts of ammonia from urea which results in an alkaline urine and a tendency to the formation of calculi containing calcium magnesium carbonate and phosphate

Symptoms The symptoms of colon bacillus infection are of two types local and constitutional The *local symptoms* are determined by the particular organ infected—gallbladder bile ducts appendix urinary bladder kidney—more than by the organism concerned and detailed descriptions of these conditions will be found in appropriate sections of this book The *constitutional* symptoms are most marked in cases of peritonitis suppurative pylephlebitis cholangitis acute pyelonephritis or whenever there is bacteremia In children and adults severe shaking chills followed by episodes of high fever malaise headache nausea and sometimes vomiting are the rule Relative bradycardia may be seen Where there are purulent foci leukocytosis with a predominance of polymorphonuclear cells is marked and anemia develops rapidly In newborn infants the picture of sepsis with these organisms which may involve middle ears lungs kidneys and meninges may be one of prostration with subnormal temperature vomiting diarrhea and convulsions although fever leukocytosis jaundice and hepatosplenomegaly are often seen in instances of ascending infection from the umbilical stump Although acute pyelonephritis is generally associated with prominent constitutional symptoms many urinary tract infections remain chronic throughout and may manifest themselves only by fatigue backache and slight malaise

Superficial infections with *Ps aeruginosa* are relatively asymptomatic but when invasion occurs this organism produces serious toxic manifestations In infants in whom infection of the gastrointestinal tract may cause ulceration at any point along its course from mouth to anus prostration vomiting diarrhea abdominal distention with paralytic ileus and a tendency to pancytopenia may be observed In bacteremic cases skin lesions may be primary or metastatic Most characteristically these consist of a bright pinkish areola surrounding a gangrenous center (*ecthyma gangrenosum*) Other types of rashes including rose spots have been observed particularly in certain cases where the clinical picture has resembled that of typhoid fever In adults bed sores or chronic foci of infection in the genitourinary tract may serve as the sources of bacteremia which is apt to give severe chills high fever and prostration Meningitis is the commonest metastatic complication of bacteremia but may also develop as a result of the accidental introduction of organisms on lumbar puncture or ventricular drainage Pneumonia and arthritis are also seen as local manifestations of *Pseudomonas* infection Ulceration of the cornea due to *Ps aeruginosa* usually leads to a destructive panophthalmitis unless vigorously treated Although leukopenia anemia and thrombocytopenia have been observed in severe cases of *Pseudomonas* infection moderate leukocytosis occurs more frequently

Diagnosis In local infections the colon bacillus may be suspected from the fecal odor and greenish color of the pus whereas *Pseudomonas* should be considered whenever pus or discharges have a bluish or greenish yellow color Diagnosis can be made only by bacteriological methods the finding of gram negative bacilli on smear and their isolation on culture of the local lesion Blood culture should be performed in cases with high fever and a properly collected specimen of urine examined and cultured in all cases of suspected urinary tract infection

Prognosis In severe infections due to the colon group prognosis depends on several factors First pure colon bacillus infections have a better prognosis than mixed infections particularly in the abdomen where the presence of pyogenic cocci and anaerobic bacilli adds greatly to the severity of the disease Second the age and condition of the patient make a tremendous difference infants and elderly patients do badly Third the type of anatomical difficulty which gives rise to the infection has a marked bearing on prognosis

In the urinary tract the degree of destruction of the renal parenchyma and the possibility of remedying the obstruction to urinary flow will influence the outcome of the acute attack and the ultimate course of the disease Urinary infections in diabetic patients and infections due to *Proteus* or *Pyocyaneus* are apt to be resistant to therapy

Treatment The treatment of these infections should be of three types first general supportive measures second antimicrobial therapy and third therapy of the local infection The last frequently calls for surgical intervention in the case of intra

abdominal infection In such cases as in other types of generalized or severe infections with the gram negative bacilli intensive chemotherapy is essential

Supportive measures are particularly important in the early phases of gram negative bacillary infections while the invasive stage is being brought under chemotherapeutic control because the potent endotoxins liberated may produce severe prostration and circulatory collapse and because most patients are either very young elderly or debilitated In addition to parenteral fluids and blood transfusions to combat anemia and support the circulation the administration of adrenocorticotropic hormone cortisone or hydrocortisone in combination with a vasopressive agent like l norepinephrine for two to three days may enable properly selected very ill patients to survive the initial toxicity of the infection

The intelligent use of *antimicrobial therapy* in gram negative bacillary infections demands close collaboration between the physician and the laboratory because of the varied drug susceptibilities of members of this group of organisms and the tendency for resistant strains to emerge during treatment For these reasons cultures should be obtained and the effect of the available drugs upon the strain in question determined *in vitro* whenever possible In severe infections of the abdominal or pelvic viscera which are apt to be mixed infections the combination of penicillin and one of the drugs effective against bacteria of the coliform group (streptomycin chloramphenicol or one of the tetracyclines in doses of approximately 30 to 50 mg per kg) should be used until an accurate bacteriological diagnosis can be made A tetracycline drug or streptomycin and a sulfonamide represent the best drug regimens for the early treatment of known infections due to *E coli* or Aerobacter in the absence of laboratory data on drug susceptibility With Proteus infections the situation is more difficult and streptomycin with chloramphenicol (or a sulfonamide) probably is the most reasonable initial therapy However if a therapeutic response is not obtained after forty-eight hours of adequate dosage another drug of the group listed above should be tried Polymyxin B (Aerosporin) is at present the most effective antimicrobial drug for the treatment of systemic infections due to *Pseudomonas aeruginosa* but because of its potential toxicity it should not be used unless a specific bacteriological diagnosis has been made Average dosage is 2 5 mg per kg Neomycin is the most useful drug for elimination of pathogenic *E coli* from the stools

Management of urinary tract infections should include the following

1 Evaluation of the anatomical situation
2 Relief of obstruction if possible and care of disease of the large bowel
3 Forcing of fluids to maintain a free flow of urine thus washing out pus and cellular debris whenever this is compatible with chemotherapy
4 Adequate chemotherapy to relieve acute symptoms and cure the infection if possible
5 Careful follow up study in order to recognize and treat recurrences promptly

The treatment of chronic urinary tract infections should be carried out in cooperation with a skilled urologist and planned after careful bacteriological studies of the organisms involved because of the tendency to recurrence or the development of resistant organisms unless the mechanical factors responsible for the infection can be controlled

The local treatment of chronic infections involving the skin wounds ears and bronchial tree in which gram negative bacilli may be involved cannot be considered in detail here but methods are constantly improving The development of enzymatic therapy with streptodornase and streptokinase has represented an important advance in this field particularly in the treatment of *Pseudomonas* infections Application of sulfonamides or penicillin to the skin should be avoided because of the danger of sensitization of the patient to their subsequent systemic administration

Prevention The prevention of serious infections of this type consists mainly in the prompt recognition and treatment of abdominal disease such as appendicitis and cholecystitis the proper handling of labor scrupulous cleanliness in the handling of open wounds and prompt institution of tidal drainage in neurological conditions in which control of the sphincters is lost for more than a few days Above all it is important to consider infections of the urinary tract as potentially serious since they are prone to recur to induce the formation of calculi and to produce renal damage and even severe hypertension in some cases

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Klebsiella Infections (Friedlander's Bacillus)

History The organism was discovered by Friedlander in 1882 It was first described as a coccus and as the cause of pneumonia This gave rise to considerable confusion and to a bitter controversy especially with Fraenkel The controversy was essentially resolved in 1886 by Weichselbaum who came around to the view now generally held namely that pneumococcus is the chief etiological agent of pneumonia and that Friedlander s bacillus is the cause in a small percentage of cases

Bacteriology Friedlander s bacillus *Klebsiella pneumoniae* (synonyms *Bacillus mucosus capsulatus B friedlanderi B pneumoniae Pneumobacillus Encapsulatus mucosus*) is an encapsulated short plump nonmotile gram negative rod which grows to form mucoid gelatinous colonies on agar and a slimy surface pellicle in broth Organisms of the genus *Klebsiella* are often difficult to differentiate from other encapsulated species of the tribe *Escherichia* particularly those of the genus *Aerobacter* There is considerable overlapping not only in the biochemical reactions which are still the most useful for clinical purposes but also in the groups which are based on the O or somatic antigens and in the types based on capsular antigens More than 77 capsular types have already been identified

Occurrence and Pathogenicity Klebsiella occurs in the respiratory passages of from 2 to 25 per cent of normal persons in the normal intestinal tract even in infants and in the respiratory tract of mice guinea pigs and rabbits Klebsiella has been found in soil dust air and water The microorganisms are pathogenic for man producing characteristic acute and chronic pulmonary infections and also suppurative infections in the upper respiratory passages in the intestinal biliary genital and urinary tracts and in serous cavities and meninges Klebsiella can give rise to septicemia and pyemia The microorganisms produce septicemia and widespread lesions when injected into mice guinea pigs and rabbits

KLEBSIELLA PNEUMONIA

Definition Klebsiella pneumonia is a specific acute infectious disease caused by *Klebsiella pneumoniae* and characterized by *massive mucoid inflammatory exudate of* lobar or confluent lobular distribution in one or more lobes of the lung with a tendency to necrosis and abscess formation It is commonly known as Friedlander s pneumonia

Incidence and Distribution Klebsiella pneumonia constitutes from 0 6 to 13 per cent of all cases of pneumonia in different series averaging 1 1 per cent in over 17 000 cases (Julianelle) It has been encountered in most parts of the world and in all seasons The disease is usually sporadic *but contact cases and epidemics have occurred*

Bacteriology Klebsiella has been found in pure culture during the first days of the disease in sputum lung and pleural fluids and in blood cultures and in direct smears and cultures from the blood and lungs at autopsy in rapidly fatal cases The pneumonias are caused predominantly by type A strains which are found in about two thirds of the cases Type B is next in frequency

Predisposing Factors Pneumonia due to Klebsiella has its greatest incidence between the ages of forty and sixty years Chronic alcoholism malnutrition and general debility are encountered *frequently in these* cases Antecedent simple upper respiratory infections are relatively infrequent The disease may occur as a secondary *infection* following pneumonia due to other organisms particularly pneumococci or contrariwise it may be followed by infections with other organisms

Morbid Anatomy The involved lung is heavy voluminous and noncrepitant with massive consolidation (lobar or confluent lobular) of one or more entire lobes Plaques of fibrin are found on the pleural surfaces The cut section usually has a smooth but mottled gray red or red brown surface from which thick stringy mucinous exudate often oozes as if under pressure The underlying lung often reveals soft areas in which alveoli appear liquefied and replaced by the mucinous exudate In older lesions there may be gray green purulent exudate with large areas of abscess forma

tion Histologically the outstanding features are the necrosis of alveolar tissue the enormous numbers of encapsulated bacilli and the exudate consisting of polymorphonuclear large mononuclear (alveolar epithelial cells or monocytes) and erythrocytes in varying proportions with only a small amount of fibrin The phagocytosis of klebsiella in an experimental pneumonic lesion may be seen in Figure 20 (page 116) in the section on Pneumococcal Pneumonia

Symptoms and Course The onset is usually with chill pleuritic pain cough and bloody sputum Profound prostration sets in early and delirium and distention are common Dyspnea and cyanosis also occur early and may be intense Sputum is usually copious but is often raised with difficulty because of its mucoid and sticky character it may appear rusty but is more often brick red or bloody and gelatinous resembling currant jelly Organisms are abundant in smears of such sputum Hemoptysis vomiting and diarrhea are frequent and jaundice is present in many of the severe cases Erythemas sometimes scarlatiniform occur and patients with bacteremia may have petechiae Herpes rarely occurs

Signs of consolidation may be made out early but more often the classic signs are absent and there may be only dullness and muffled breath sounds even when massive density is visible in the roentgenogram This is presumably due to plugging of bronchi with viscid exudate Moist rales may be heard over some areas of the lung Involvement of the upper lobes or of multiple lobes is more frequent than in pneumococcal pneumonia The fever may be sustained or irregular but usually ranges lower than in cases due to pneumococci

The disease may run a fulminating course ending fatally in twenty four to thirty six hours The average duration in Bullowa s cases was about five and a half days Death is usually associated with peripheral vascular collapse pulmonary edema or extreme respiratory distress without pulmonary edema Recovery is sometimes by crisis but more often it is by lysis and then may frequently be followed by the chronic type of pulmonary infections to be described later

Laboratory Findings The chief distinctive finding is the large number of characteristic bacilli in smears of the sputum Agar cultures made of the sputum directly yield the characteristic mucoid colonies usually in pure culture Blood cultures yield the same organisms in more than half of the cases and the organisms may be obtained almost regularly in pure culture by lung puncture or from pleural exudates even when the blood culture is sterile Total leukocyte counts below 6000 per cu mm occur in more than one third of the cases In other cases there is a moderate leukocytosis with total counts reaching 25 000 or 30 000 per cu mm in the presence of purulent complications

Roentgenograms usually show marked density developing early Areas or rarefaction may appear later indicating abscess and cavity formation which in patients who survive long enough then shows evidence of healing and fibrosis

Complications The commonest complication is delayed resolution with abscess formation and fibrosis of the lung (see below) Pleurisy is frequent Empyema pericarditis meningitis nonsuppurative arthritis and superinfections with other organisms notably pneumococci and hemolytic streptococci have been noted Empyema and lung abscess which does not drain properly may require surgical intervention but this should be avoided in the latter instance if possible because a chronic sinus may result

Diagnosis Klebsiella pneumonia is suspected in any case of acute pneumonia with severe prostration occurring early especially if there is bloody gelatinous sputum The diagnosis is based on demonstrating the characteristic encapsulated bacilli in smears and cultures of sputum as the only or predominant organism They may be typed directly by the Neufeld method The disease in some of its stages may simulate acute pneumonias due to other organisms particularly pneumococcus pulmonary tuberculosis acute pulmonary infarction or bronchiectasis

Prognosis The mortality in primary acute cases when untreated averages about 80 per cent regardless of whether or not bacteremia is demonstrated this has been reduced to about 40 per cent in patients treated adequately with antimicrobial drugs The mortality in chronic or recurrent cases is appreciably lower

Treatment The general and symptomatic treatment for klebsiella pneumonia is the same as for severe cases of pneumococcal pneumonia Since peripheral vascular collapse is not uncommon in klebsiella pneumonia the blood pressure should be determined frequently and norepinephrine administered promptly in the presence of hypotension Antimicrobial therapy consisting of both streptomycin or dihydrostreptomycin and chloramphenicol should be instituted at the earliest moment The strep

tomycin should be given in a total daily dosage of 2 0 gm administered intra muscularly in two equally spaced doses The chloramphenicol may be given by mouth in a total daily dosage of 3 0 gm ad ministered in divided doses at six hour intervals As the patient recovers the daily streptomycin dosage may be lowered to 1 0 gm but the streptomycin chloramphenicol therapy should be continued for a total period of at least two weeks One of the tetracycline drugs may be substituted for the chloramphenicol in the above regimen but the chloramphenicol is preferable

CHRONIC KLEBSIELLA INFECTIONS OF THE LUNGS

Definitions These are subacute or chronic infections of the lung caused by *Klebsiella pneumoniae* with a protracted and relatively benign course and expectoration of purulent nonputrid and sometimes bloody sputum Characteristically they are accompanied by abscess formation bronchiectasis and pulmonary fibrosis and exhibit a tendency to exacerbations of acute pneumonia

Occurrence, Etiology and Pathogenesis The exact incidence of these chronic forms is difficult to establish but they are much less frequent than the acute klebsiella pneumonias Probably many cases go unrecognized and are included as tuberculosis or as other chronic pulmonary infections The relation of the klebsiella to the disease is based upon finding the organism in large numbers and often in pure culture in sputum in abscess or pleural fluid or in blood cultures during acute phases Other organisms are also found in varying numbers in the later stages

Morbid Anatomy Grossly the lungs present a picture of confluent pneumonia with fibrosis bronchiectasis and abscess formation The walls of the cavities consist of bundles of collagen fibers bearing connective tissue cells without the remains of alveolar walls Bronchi showing bronchiectatic changes often blend with foci of acute inflammation and with abscesses

Symptoms and Course The disease usually begins as an acute klebsiella pneumonia with slow recovery over a period of weeks during which abscess formation and fibrosis of the lung occur In some cases there is a milder course from the start with low grade persistent fever cough with copious purulent sputum loss of weight and recurrent pleurisy The sputum is not foul unless there is a mixed infection and intermittently becomes blood streaked brick red or grossly bloody The disease may go on for several weeks and end in complete symptomatic recovery with apparent clearing of the lesions on the roentgenogram or it may persist for many months or years Chronic abscess formation and bronchiectasis with fibrosis tend to reproduce the disease and give rise to relapses and frequent hemoptysis particularly after acute respiratory infections In more than three fourths of the cases one or both upper lobes are involved

Laboratory Findings The typical encapsulated bacilli are always present in large numbers Secondary organisms including pneumococci staphylococci influenza bacilli and other common mouth inhabitants may also be abundant Bacteremia is less common in these chronic cases but positive blood cultures have been obtained during the original acute pneumonia and during exacerbations Specific antibodies may be demonstrated early and persist for a few weeks Low grade leukocytosis is the rule except during acute phases when there may be a leukopenia Roentgenograms of the chest show thin walled cavities with or without fluid and later there is fibrosis and retraction of the upper lobes simulating tuberculosis

Complications Recurrent pleurisy is frequent Empyema usually encapsulated with thick mucoid pus may occur with or without relation to abscess formation in the lung Serous effusions are encountered which may be sterile or infected and may occur in patients who have purulent empyema elsewhere Recurrences of acute pneumonia and hemoptyses are the rule Axillary thrombophlebitis with acute arthritis has been encountered Pericarditis and meningitis may occur as terminal events

Diagnosis In cases seen during the acute phase the diagnosis is made when there is slow recovery and evidence of abscess formation with copious sputum The disease may be simulated by *pulmonary tuberculosis with cavitation* Many patients with the latter diagnosis in whom tubercle bacilli are not found are shown to have chronic klebsiella infections The diagnosis depends on repeatedly demonstrating the characteristic encapsulated bacilli as the only or predominant organism in smears and cultures Staphylococcal pneumonias bronchomycoses lung abscess bronchiectasis and tumors of the lung must be considered in the differential diagnosis

Prognosis The mortality is said to be about 25 per cent Death may occur in the

original attack after a slowly progressive illness of several weeks or months or it may occur during an acute exacerbation of pneumonia with the same or other organisms or as a result of complications such as pericarditis meningitis or after operation for empyema or lung abscesses Some patients apparently recover completely while most of the others continue to have signs and symptoms for many years

Treatment Intensive antimicrobial therapy as outlined for the management of acute Klebsiella pneumonia should be employed Empyema usually necessitates rib resection which may also be necessary for large pulmonary abscesses which fail to drain Conservative treatment is recommended for abscesses in general in the hope that they will eventually drain into a bronchus In cases in which the chronic Klebsiella infection is localized to a lobe or pulmonary segment some form of excisional surgery should be considered

KLEBSIELLA SEPSIS

Definition This is a local or generalized infection caused by the *Klebsiella pneumoniae* frequently accompanied by bacteremia and associated with localized purulent infections in one or more organs

Klebsiella bacteremia is relatively uncommon and is seen less frequently than bacteremia caused by streptococci staphylococci colon bacilli meningococci or pneumococci Several types of generalized Klebsiella infections with bacteremia are described (1) a pure bacteremic type which has an acute and rapidly fatal course (2) a pyemic type with multiple abscesses in many organs (3) bacteremia with symptoms referable predominantly to one organ and (4) one which is secondary to infection with other organisms

Portal of Entry The organisms may gain access to the blood stream from any of the following foci the middle ear the lungs particularly when there is thrombophlebitis of the pulmonary vein the intestinal tract commonly in infants the liver especially when there is thrombophlebitis of the hepatic or portal vein the urinary tract the genital tract notably the prostate in males the adnexa or the puerperal uterus in females A large proportion of the cases are so-called cryptogenic and the original focus cannot be determined even at autopsy Little is known concerning the type distribution of klebsiella in these cases The organism is recovered in pure culture from the blood and from foci of suppuration and frequently from the urine

Occurrence and Predisposing Factors Many of the cases occur in infants children and young adults of both sexes differing in these respects from the pneumonias Alcoholism cirrhosis of the liver and diabetes are particularly frequent in the adult cases

Morbid Anatomy The dominant feature is the finding of metastatic abscesses in the liver lungs and kidneys Only those in the lungs are characteristic The pus in the abscesses is usually mucoid and tenacious and the characteristic organisms are readily found in large numbers in smears and are usually in pure culture Ulcerative endocarditis meningitis and involvement of serous cavities are sometimes encountered

Symptoms and Course The onset may be abrupt with severe chills or may be insidious with high continuous or intermittent fever and general malaise with or without chills Vomiting and diarrhea are common Rashes occur and may be scarlatiniform maculopapular or petechial in character There is an acute fulminating type described (Blumer and Laird) with a hemorrhagic septicemia in which intestinal symptoms predominate and in which changes in the intestine similar to those of typhoid fever are found at autopsy In some cases particularly in adolescents the course may simulate that of typhoid fever in every respect including the leukopenia In others the picture is dominated by some local lesion such as abscesses of the kidney lungs prostate or liver or by a cholecystitis with ascending infection or there may be perforation of the intestine with peritonitis In the cases with liver abscesses jaundice may be prominent The disease may be of short duration or last for several weeks Meningitis or endocarditis may occur terminally

Diagnosis This depends on finding the klebsiella in blood cultures or on demonstrating the organisms in characteristic pus from metastatic lesions

Prognosis The mortality is high but except in cases with pyemia recoveries are recorded in all types of cases including some which have shown a persistent bacteremia for some time The prognosis is particularly favorable in cases in which there is a predominant focus such as the prostate which is accessible to surgical drainage

Treatment Streptomycin along with chloramphenicol should be given in full doses as in the cases of pneumonia Accessible foci should be drained surgically

MAXWELL FINLAND

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Bacillary Dysentery

Definition Bacillary dysentery is an infectious disease characterized by pyogenic inflammatory lesions of the large bowel The cardinal clinical symptoms are diarrhea tenesmus and abdominal cramps In severe cases mucus and pus are characteristically found in the stools Blood may or may not be present The causative organisms belong to the genus Shigella hence the use of the term Shigellosis to include all types of infection caused by them The disease is widespread throughout the world but is particularly prone to appear in epidemic form in the tropics

History Bloody diarrhea accompanied by tenesmus and abdominal pain was recognized as a clinical entity by Hippocrates in the fourth century B C Herodotus attributed the defeat of the Persian Army in 380 B C in part to dysentery and since that time it has been an important scourge of military campaigns Only in World War II was field sanitation sufficiently developed to prevent epidemic outbreaks of the disease The separation of amebic and bacillary dysentery on clinical epidemiological and pathological grounds took place in the latter part of the nineteenth century In 1898 Shiga identified *Shigella dysenteriae* Type I as the causative agent in an outbreak of the disease occurring in Japan and in the course of the next twenty years Flexner Sonne and Schmitz isolated related organisms from patients suffering from dysentery in other parts of the world

Etiology The causative agents of bacillary dysentery are bacteria belonging to the genus Shigella These organisms are slender nonsporulating gram negative rods which are neither motile nor encapsulated They are facultative anaerobes which show optimum growth at 37° C and are not fastidious in their growth requirements On the basis of biochemical and antigenic studies several distinct species have been recognized within the genus

The more important pathogens are *Shigella dysenteriae* Type 1 (Shiga bacillus) and Type 2 (Schmitz bacillus) *Shigella flexneri* (Flexner subgroup of paradysentery bacilli multiple antigenic types) *Shigella boydii* (Boyd subgroup of paradysentery bacilli multiple antigenic types) and *Shigella sonnei* (Sonne bacillus)

Of these species only *Shigella dysenteriae* Type 1 produces a soluble heat labile exotoxin This is neurotoxic in nature and its relation to the pathogenesis of the disease remains uncertain The cell substance of dysentery bacilli (in common with other gram negative organisms) contains a relatively heat stable endotoxin which when injected parenterally into small mammals causes diarrhea weight loss and inflammation of the gastrointestinal wall which may progress to actual ulceration While it is plausible to assume that the release of this endotoxin in the gut wall as a result of autolysis of the bacterial cells is related to the production of the specific lesions direct proof of this is lacking The pathogenesis of the disease process is not clear

Epidemiology The portal of entry for the dysentery bacillus is the gastrointestinal tract the usual vehicle is feces contaminated food water or fingers During the acute stage of the disease the organisms are excreted in large numbers in the liquid stools This process may continue during convalescence or even into the period when the patient has become asymptomatic Dysentery in epidemic form is likely to occur at times when large groups of people are massed together under conditions of defective sanitation *e g* armies in the field refugee camps overcrowded asylums for the mentally deficient Direct person to person transfer of fecal material is presumably the most important method of spread under such conditions (Watt) Tropical conditions by favoring the mechanical spread of the disease by flies and other arthropods are propitious for the development of epidemic disease Although in temperate climates the disease tends to appear in endemic rather than epidemic

form it is nonetheless widespread In these conditions the symptomless carrier is presumed to represent the usual source of infection The incidence of the disease in these areas is usually greater in the warmer months of the year

Morbid Anatomy Bacillary dysentery is a pyogenic inflammation of the mucous membrane of the large bowel which may extend to involve the lower ileum as well The earliest changes are generalized hyperemia and edema of the mucosa Focal ulceration occurs as the surface tissue becomes necrotic and sloughs off These ulcers show sharp well defined margins in contrast to the undermining lesions of amebic dysentery In bacillary dysentery the ulcers do not extend as a rule beyond the muscularis mucosae and only rarely go on to perforation The infectious process is essentially *local* being limited to the gut wall and invasion of the blood stream is an uncommon finding Healing takes place by the formation of granulation tissue which is often pigmented Scar tissue formation is common only if the ulcers are unusually deep and extensive

Pathological Physiology and Biochemistry The frequent passage of copious liquid stools as a result of the inflammatory process involving the large bowel causes a significant loss of both water and electrolytes As a result of the relatively greater loss of base (sodium and potassium) in the form of intestinal secretions acidosis develops which is accentuated if the patient is unable to take food by mouth If fever is present the insensible loss of water increases and dehydration is correspondingly more marked In severe cases appreciable amounts of blood may be lost with the stools but in the uncomplicated infection it is rare for this to progress to the point where significant anemia develops In interfering with the proper absorption of food stuffs long continued diarrhea results in significant malnutrition

Clinical Manifestations The incubation period probably varies from one to six days with a median of approximately forty eight hours Incubation periods of less than twenty four hours have been reported but are rare The magnitude of the infecting dose and the general physical condition of the patient are factors which probably affect it

The clinical severity of bacillary dysentery varies greatly from the very acute case in which the severity of the diarrhea and the prostration of the patient simulate cholera to the mild one in which they may be no more than slight diarrhea for a few hours with the passage of no blood and but little mucus The great majority of clinically recognized infections fall between these extremes

The *onset* is usually abrupt Fever and abdominal cramps are the initial complaints Chilly sensations and even frank chills are occasional symptoms at this stage Diarrhea follows within a few hours The *stools semisolid at first rapidly become* watery and in all but mild cases are accompanied by the passage of mucus and pus and less frequently blood The patient may have watery bowel movements as often as four to five times an hour After a few hours the frequency of movement becomes less generalized abdominal cramps are succeeded by tenesmus and the relatively scanty movements may begin to show gross blood Headache lassitude and general prostration are prominent features of the severer cases Nausea is a common complaint Vomiting may occur but is rarely protracted

Physical examination at this time shows *an anxious patient complaining of general*ized abdominal discomfort and scalding bowel movements Evidence of dehydration dry tongue and skin and drawn facies may be apparent in the more severe cases Abdominal tenderness most marked in the lower quadrants is usually found and at times is accompanied by generalized muscle spasm Occasionally this is sufficiently localized in the right lower quadrant to suggest acute appendicitis Sigmoidoscopic examination reveals hyperemia and edema of the bowel wall accompanied by spasm and rigidity Injection of the lymph follicles and areas of purulent exudate may often be seen as well A normal or moderately elevated leukocyte *count* (10 000 *to* 15 000 cells per cu mm) is the usual finding Leukopenia is occasionally encountered if this is marked and primarily granulocytic the prognosis must be guarded

In the case of average severity to which supportive therapy is given the disease runs its course over a period of a week or ten days Concomitant with a diminution in the daily number of stools is a decrease of tenesmus and a return of appetite and a *sense of well being Mild diarrhea may* continue for some days after the tenesmus and anorexia have disappeared In light cases strength and weight are regained in a matter of days if the attack has been severe the return to the normal state of well being may take several weeks If the infection is complicated by preexisting mal

nutrition or debility or if opportunity for supportive therapy is not available at the onset convalescence is correspondingly prolonged

Conjunctivitis upper respiratory symptoms and signs of meningeal irritation are occasionally met with during the acute stage of the disease In the last instance lumbar puncture reveals a normal cerebro spinal fluid Toxic encephalitis and peripheral neuritis have been reported as rare complications of *Shigella dysenteriae* Type 1 infections

Arthritis has been reported as a late complication in a small (1 per cent) proportion of cases It usually occurs during the second or third week after onset of the acute disease at a time when complete recovery is about to be attained The process involves the larger joints in single or multiple fashion Migratory polyarthritis is less common Usually the inflammatory condition subsides completely and spontaneously within the course of a fortnight

In a minority of instances the disease may progress from the acute to the chronic state Low grade irregular fever may persist for some weeks accompanied by intermittent bouts of mild diarrhea during which the stools show mucus in varying quantities but rarely significant amounts of blood Although it has been suggested that this condition predisposes toward the development of ulcerative colitis and ileitis an etiological relationship has not been proved

Diagnosis The abrupt onset of fever abdominal pain and diarrhea accompanied by the passage of mucus and blood strongly suggests the diagnosis of bacillary dysentery particularly if similar cases are encountered simultaneously in the same household or community Atypical cases present more difficulty Microscopic examination of the stool should always be done if possible The gross findings of mucus and blood may be confirmed by examination of coverslip preparations of mucus previously emulsified in saline The exudate of bacillary dysentery is highly cellular with a great predominance of polymorphonuclear cells as opposed to the mononuclear exudate characteristic of protozoal infections

The specific diagnosis is made by the isolation and identification of the etiological agent Cultures are best taken either by sigmoidoscopy or by means of the rectal swab technique If stool culture must be resorted to the specimen should be brought promptly to the laboratory and cultured as soon as possible Since the organisms are found in greatest numbers in the mucous exudate flecks of this material should be selected for culture Of the various differential media used for the isolation of dysentery bacilli S S agar (Difco) and desoxycholate citrate agar are the most useful Once suspected colonies have been isolated they may be identified by the proper biochemical and serological techniques notably fermentation of carbohydrates and agglutination by specific antiserums Since even in the best of circumstances it is not always possible to isolate dysentery bacilli from clinical cases that are otherwise typical a negative culture does not exclude the diagnosis

During the second week of the disease agglutinins appear in the patient s blood The serological diagnosis by the demonstration of these antibodies is unsatisfactory however since they develop irregularly and relatively late in the course of the disease In addition many healthy persons have significant agglutinin titers as a result of previous contact with the organisms This is particularly true in areas in which dysentery is widespread as in the tropics

Differential Diagnosis The differential diagnosis must include other infections characterized by diarrhea In contrast to bacillary dysentery amebic dysentery usually occurs sporadically the onset is insidious and the patient is not incapacitated in the early stages of the disease which however usually progresses to chronicity Sigmoidoscopic examination reveals the typical lesions while the finding of the specific amebas in the stools confirms the diagnosis Cholera may usually be excluded on epidemiological grounds as well as by the absence of excessive vomiting and of typical ricewater" stools containing cholera vibrios Occasionally typhoid and paratyphoid fevers may be accompanied in their early stages by diarrhea but the onset is usually much less abrupt The diarrhea caused by salmonella food infections comes on suddenly and is often severe in addition the cellular exudate may resemble that of bacillary dysentery In such cases the differential diagnosis depends upon the isolation and identification of the etiological agent Food infection due to streptococci or staphylococci may usually be differentiated on the basis of the shorter incubation period more vomiting and the absence of mucus and cellular exudate in the stools

Prognosis In ordinary circumstances bacillary dysentery tends to be an acute self limited disease which usually runs its course over a period of ten days without

an appreciable case fatality rate Outbreaks of bacillary dysentery have been reported however in which the case fatality rate has been as high as 30 per cent In general prognosis in any individual case depends upon three factors (1) the species of infecting organism (2) the age and general physical condition of the patient at the time of infection and (3) the opportunities for supportive treatment and chemotherapy

Shigella dysenteriae Type 1 has long been credited with causing a particularly virulent type of the disease which in Japan and India has been attended by a high mortality rate Infections with this organism are fortunately rare in the United States and Canada In these countries the predominating bacteria *Shigella sonnei* and various types of *Shigella flexneri* generally give rise to a milder form of the disease

Persons in the extremes of life infants and the aged are less resistant to the disease and among them the case fatality rate is appreciably higher Further persons debilitated by acute or chronic malnutrition hardship privations or other unfavorable conditions of living are particularly susceptible to its ravages These environmental factors are undoubtedly responsible in part at least for the high case fatality rate accompanying epidemics of bacillary dysentery in the Far East

If adequate supportive therapy is made available for the patient early in the course of his disease the prognosis is greatly improved Under favorable conditions chemotherapy may play an important role in controlling the infection

The importance of all these factors is borne out by the remarkably low case fatality rates observed in the British and American Armed Forces during the latter part of World War II

Treatment The rational aims of the treatment of bacillary dysentery are (1) supportive and symptomatic to maintain the patient s strength and to relieve his symptoms (2) correction of the pathological disturbances of salt water and protein metabolism (3) eradication of the infectious agent by means of antimicrobial agents

General Management During the acute phase of the disease complete bed rest is indicated The use of a diaper of absorbent cotton or cellulose instead of a bedpan saves the patient from unnecessary exertion Purging should be avoided since it merely increases the patient s discomfort In severe cases expert nursing care is of vital importance The patient should be isolated kept warm and screened from flies Sanitary precautions as for any enteric infection must be maintained and particular attention should be paid to the sterilization of excreta and of soiled bed linen

The abdominal pain and discomfort may usually be relieved by the application of heat (hot water bottles stupes and so forth) to the abdomen plus the judicious use of sedatives and antispasmodic drugs According to Thompson White and Schafer the following prescription is particularly useful

	Gm or Ml
Tincture of belladonna	8
Sodium bromide	10
Elixir phenobarbital to make	60
Directions 1 teaspoonful every four hours	

In some instances these measures will not control the discomfort Though the routine use of paregoric and other opiates is contraindicated because of the artificial intestinal stasis that they cause a gravely ill patient can occasionally be tided over the acute episode by the parenteral administration of codeine (45 mg) or morphine sulfate (10 mg) which will usually give him a few hours comfort

Dehydration and acidosis resulting from loss of base in the intestinal secretions must be combated vigorously by use of supplemental parenteral fluids if an oral intake adequate to produce a daily urinary output of 1500 to 2000 ml cannot be maintained In the average case the daily intravenous administration of 1500 ml of physiologic saline (9 gm of sodium chloride per liter) to which 75 gm of dextrose has been added suffices to correct the electrolyte balance and adds much to the patient s comfort Severe cases require more parenteral fluid which should be given in the form of 5 per cent dextrose in distilled water Rarely is the acidosis so severe as to require the use of supplementary sodium lactate

If the patient shows evidence of incipient vasomotor collapse or shock coupled with hemoconcentration plasma should be given in amounts adequate to restore the hematocrit reading to normal It is rarely necessary to give more than 500 ml for this purpose It is important that dehydration be relieved *before* or at least *simultaneously* with the administration of the plasma In the occasional patient who develops a significant anemia secondary to blood loss in the stools whole blood transfusions are indicated

The diet during the acute stage of the disease is best limited to clear fluids given warmed and in small quantities With the

return of appetite and feeling of well being a bland low residue diet containing adequate protein and vitamins is given The return to a full diet should be made gradually and cautiously In severe protracted cases the oral or parenteral administration of supplementary vitamins may be advantageous

Antimicrobial Therapy The broad spectrum antimicrobials the tetracyclines and chloramphenicol are markedly effective in the treatment of bacillary dysentery The recommended dosage schedule for these drugs is 2 0 gm initially followed by 1 0 gm every twelve hours This usually results in prompt disappearance of clinical manifestations and a rapid conversion from positive to negative cultures It is advisable to continue specific therapy for forty eight to seventy two hours after the acute diarrheal manifestations have subsided The occurrence of relapses due to the emergence of drug resistant organisms has not constituted a significant problem as yet It should be noted that the tetracycline drugs also exert a definite effect in amebic dysentery This effect is apparently not exerted directly on the ameba but is a result of the influence of the drug on the intestinal bacterial flora The fact that an undiagnosed dysentery appears to respond promptly to tetracycline therapy thus does not necessarily indicate that it is caused by Shigella Since the tetracyclines are not considered the most satisfactory therapy for amebic dysentery if the possibility of amebic etiology is strong the patient should receive other therapy (see Amebic Dysentery)

The effectiveness of the sulfonamides in the treatment of bacillary dysentery has been considerably reduced in recent years by the frequent occurrence of drug resistant strains In the past sulfadiazine has proved to be the most effective of these compounds

Prevention Although it is manifestly important to detect isolate and treat all cases of the disease as soon as possible the prevention of bacillary dysentery by the eradication of the etiological agent is rendered impracticable by the existence of a significant number of asymptomatic carriers of dysentery bacilli Strict attention to personal hygiene is most important Adequate sanitation proper safeguarding of food and water supplies effective disposal of sewage and fly control are the most valuable public health measures Bacterial vaccines have not been effective Chemoprophylaxis employing the tetracycline drugs should be effective in theory but preliminary reports have not been encouraging The usefulness of sulfadiazine as a chemoprophylactic agent has been limited by the rapid emergence of drug resistant strains

F S CHEEVER

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Cholera

Definition Cholera is an acute infectious disease caused by *Vibrio comma* in which the primary seat of the infection is in the gastrointestinal tract It is characterized by diarrhea vomiting and dehydration which are extremely severe in typical cases

History and Geographical Distribution Cholera has been known for centuries in India whence it spread to China in the seventeenth century A number of pandemics occurred during the nineteenth and early twentieth centuries The United States was invaded repeatedly but after 1873 practically all cases were stopped at seaports In recent years few cases have been brought to this country During and after World War I epidemics occurred in Europe During World War II there were extensive epidemics in the Far East and smaller outbreaks in the Near East but the disease did not reach Europe or the Americas

Cholera is always present in the region of the lower Ganges River in India Its distribution is potentially world wide Since World War II however as the result of improved sanitation and enforcement of the International Sanitary Regulations cholera has appeared only briefly outside India and Pakistan

Etiology The specific cause of cholera is the *Vibrio comma* (*V cholerae*) of Koch (1883) The organism is a short curved bacillus with a terminal flagellum It is aerobic grows on ordinary media is motile easily stained by the usual methods and is

gram negative It is readily dissociated into R and S forms Both H and O antigens are present The cholera bacillus is one of a large group of vibrios and its identification necessitates the use of a specific agglutinating serum or of special cultural procedures when agglutination fails as occasionally happens

Epidemiology The etiological agent may persist in nature in favorable circumstances for a few days but it dies out in stools in one or two days For this reason infection generally can be traced to patients in the immediate neighborhood The existence of subclinical infections in the community probably explains the often apparently haphazard distribution of clinical cases It is doubtful that true carriers exist although convalescent patients may pass virulent organisms for a short time The most important sources of infection are patients in the incubation stage and those with mild symptoms Cholera is acquired by the ingestion of food or drink contaminated by feces which contain the vibrio Contaminated water is one of the most important means of spreading the disease Flies may play an important role The development of epidemics is seasonal being favored as a rule by high temperature high relative humidity and intermittent rains Unless effective control is exercised an epidemic rapidly spreads through an unprotected population moving along lines of communication such as railway steamship and air routes Cholera is not however as readily communicable as was formerly thought for many exposed persons escape infection

Morbid Anatomy The striking changes are the result of extreme dehydration Rigor mortis is unusually marked Dryness and shrinkage are everywhere apparent but in general inflammatory changes are absent The blood is thick and scanty The serous membranes have the look of ground glass and are somewhat sticky The intestinal wall is cyanotic and congested The lumen contains much grayish opalescent liquid often with no trace of fecal matter Large areas of mucosa may be lost but localized ulceration is not present The lymphoid tissue of the ileum is somewhat prominent The kidneys may show marked congestion

Pathological Physiology and Chemistry The cholera vibrio has its principal localization in the ileum Organisms may be found in small numbers in the lungs and other organs but they are seldom if ever demonstrated in the blood Cholera vibrios produce no exotoxin and their effects are attributed to the liberation of a powerful endotoxin The principal immediate effect of the infection is precipitate loss by the body of large amounts of fluid and salts as the result of profuse diarrhea and vomiting The extraction of fluid from blood tissue spaces and tissues in turn is rarely equalled in any other condition except some cases of infantile diarrhea and extreme hemorrhage The tissues become desiccated and the blood is concentrated to a high degree Such extreme values may be encountered as 1 070 for specific gravity 20 gm per 100 ml for hemoglobin concentration 7 000 000 per cu mm for erythrocyte count and 75 for erythrocyte volume percentage The concentration of plasma proteins is also increased These alterations in the blood have a profound effect on the circulation The blood pressure is greatly reduced and the cardiac output is much decreased In part at least because of these circulatory changes renal function is gravely impaired

Chlorides are lost with the fluid of vomitus but this loss is overbalanced by that of bases principally sodium from the bowel The resulting shift in the acid base balance is accentuated by the retention of acid which results from renal insufficiency Values as low as 7 1 have been recorded for *p*H and 138 milliequivalents per liter for total base in the blood Urea and other nitrogenous substances are also retained as a result of renal insufficiency After the liberal intravenous administration of fluids even though no alkaline solution is given alkalosis tends to be present for a time during recovery In most cases death in the early stage is chiefly the result of dehydration while in the later stages it is due to renal insufficiency An attack of cholera confers only limited immunity to subsequent infection

Symptoms The incubation period is usually only one to three days sometimes as many as five In occasional instances premonitory symptoms of depression lack of energy and simple diarrhea occur The onset is usually sudden It is characterized by voluminous watery stools copious vomiting and great prostration In many cases the speed with which the symptoms attain overwhelming proportions is striking Stools are passed with great frequency and soon lose all fecal character They are grayish and contain clumps of degenerating epithelial cells and mucus but little if any blood and no pus The absence of tenesmus is often noted Vomiting may occur suddenly without nausea or retching After

a time the vomitus resembles the stools As dehydration becomes marked there is great thirst but almost nothing taken by mouth can be retained The features become gaunt and pinched and the eyes sunken The skin is cyanotic and shriveled Muscular cramps may be widespread and exceedingly painful The voice becomes thick and feeble A marked tachycardia develops and the pulse may be hardly perceptible The blood pressure falls the systolic level often reaching values below 60 mm of mercury Venesection may result in only slight bleeding The excretion of urine is diminished and may cease In severe cases uremia often develops The skin temperature usually falls below normal although the rectal temperature may be normal or even elevated unless the patient is in a state of complete collapse Unless uremia develops the mind remains clear although patients are usually extremely apathetic Complications other than those directly related to the disease are not common or characteristic They are usually related to the previous poor health of the patient as in the instances in which clinical signs of avitaminoses appear or to poor treatment Occasionally secondary infections may occur such as those causing parotitis

Of great practical importance is the fact that in epidemics cases occur in which only malaise and simple diarrhea are present throughout the course

Diagnosis Information that there is cholera in the area in which a patient lives or from which he has recently come should suggest the possibility of cholera The clinical picture is highly characteristic in ordinary cases and typical stools are highly suggestive In differential diagnosis confusion may arise over acute bacillary dysentery food poisoning heat exhaustion some forms of malaria (especially *falciparum* malaria) and other conditions associated with diarrhea and shock Mild cases of cholera masquerading as dysentery or food poisoning may be overlooked They are extremely dangerous for the public health The ordinary clinical laboratory examinations of blood urine and stool are not very helpful

The specific diagnosis of cholera is made by identification by agglutination of *V comma* derived from passed stools or better from samples obtained from the rectum Characteristic forms seen in smears stained with dilute carbolfuchsin are suggestive but the finding requires confirmation The organism may grow poorly or not at all on media usually used for other intestinal pathogens Cultures should be made from fresh specimens using peptone water at pH 8 4 After incubation at 37° C for six to eight hours the surface growth in which vibrios are concentrated if present should be examined microscopically If suggestive forms are found subcultures are made by streaking on nutrient or infusion agar After twenty four hours suggestive colonies should be tested by the slide method with agglutinating serum specific for *V comma* When positive tests are obtained the colonies should be isolated and further confirmation should be sought in the biochemical reactions of the organisms and by macroscopic tube agglutination tests

Prognosis The outcome depends greatly on the patient s previous state of health and on the promptitude and quality of medical care The course is usually short averaging three to five days Death may take place however in a few hours or only after many days The case fatality rate in epidemics among poorly treated patients is often 60 per cent On the other hand when adequate treatment is promptly given it may be as low as 5 per cent

Treatment Strict isolation is indicated for both patients and proved carriers Clothing bedding and eating utensils should be boiled Stools vomitus and (because of the danger of their being contaminated) urines should be thoroughly disinfected as for typhoid fever Because of the brevity of the acute stage the diet during that period is relatively unimportant At best patients can retain only small quantities of fluid at this time A soft diet may be given as soon as the patient desires it When the temperature is below normal the patient should be kept warm Such drugs as sedatives hypnotics laxatives epinephrine and digitalis have no place in the treatment of the usual patient The value of cholera bacteriophage is controversial No therapeutic serum which is known to be effective is available The use of antimicrobial agents is discussed later Antihistaminics have been reported to be helpful in treating the peripheral circulatory failure (and renal insufficiency) but their value is not yet established

Replacement Therapy The prompt parenteral administration of adequate amounts of solutions suitable to replace the lost water and electrolytes is crucial Failure to recognize this need or delay in action may result in the death of the patient The intravenous route is best Whole blood is not indicated in cholera The value of plasma is uncertain and the rationale of its use is obscure The main reliance should

be placed on physiological saline solution but it is customary in early cases to give limited amounts (500 to 1000 ml) of a hypertonic saline solution (sodium chloride 14 gm per liter) Only sterile distilled water which is free of pyrogens should be used to make solutions for intravenous injection It is desirable to add sufficient dextrose to make a 5 per cent solution to any solution given and 1 0 mg of thiamine chloride for each 25 gm of dextrose but this should be done so that not more than 50 gm of dextrose are given in one hour or 400 gm in twenty four hours Solutions should be given at body temperature

No rule can be given for the amount of saline solution which may be required or the period over which its administration may be necessary Patients with cholera generally need amounts of fluid rarely given for other diseases On the other hand too much fluid of any type given in too short a time may precipitate a fatal issue The patient must be closely and continuously observed The blood pressure is the most important single guide to clinical judgment Other helpful guides are the pulse rate the color and consistency of the blood and the volume of urine Signs that too much fluid has already been given are restlessness palpitation pain in the chest coughing and edema The best objective guide to treatment is the specific gravity of the blood The most convenient suitable method is the copper sulfate procedure of Phillips and his co workers The higher this value is at the start of treatment the greater is the total volume of fluid required As the specific gravity approaches its normal value (1 056 to 1 058) the rate of administration of fluid should be retarded As a rule 2 liters of fluid are needed in the first two hours and more fluid every three or four hours for sometime thereafter In the first twenty four hours 4 to 8 liters are often required and injections may have to be continued through the econd twenty four hours or longer

In many cases the loss of alkali is so great that replacement is indicated The acidosis of cholera differs from that of diabetes or nephritis In the acute stage the respiration is not a good guide to the condition Ketone bodies are not to be expected in the urine because of cholera itself The volume and reaction of the urine are important indications If practicable determinations of the blood pH carbon dioxide combining power and nonprotein nitrogen are helpful Alkali replacement may be made by the intravenous injection of a solution of sodium bicarbonate 18 gm and sodium chloride 6 gm per liter which should be prepared with the usual precautions Certain advantages including greater ease of preparation are offered by one sixth molar solution of racemic sodium lactate A good many patients need 500 ml of alkaline solution but this amount often suffices Care should be taken not to overdo the alkaline treatment In addition to sodium other electrolytes are undoubtedly lost especially phosphate and potassium The ideal replacement solution should contain such additional electrolytes as may be depleted A detailed statement however can be made only when more information about electrolyte balances in cholera and experience with the use of complex solutions become available

Chemotherapy No drug treatment should be used in cholera to the neglect of replacement therapy The good results obtainable without using antimicrobial agents render difficult the evaluation of such agents So far none of these agents has been proved to produce significantly lower fatality rates than those seen following good replacement therapy A few observers have believed that the use of sulfonamides shortened the course (it is usually very short with replacement therapy alone) When chloramphenicol or oxytetracycline is given organisms disappear early from the stools but without clinical benefit The general conclusion is that antimicrobial agents add nothing significant to what is accomplished by replacement therapy but may be of help in reducing the infectiousness of the patient for others

Prevention Since the spread of cholera is always closely associated with patients suffering from the disease the isolation of such patients and the proper disposal of their excreta and vomitus are essential Cholera is one of the few diseases subject to foreign quarantine Strict control of the water supply of food and food handlers and of flies is necessary for cholera control If the water supply is not subject to general control it should be boiled and then chlorinated In areas where cholera is present raw food should not be eaten and all handlers of food should be frequently examined and closely supervised All food should be thoroughly protected from flies and other insects Insects should be controlled by proper use of appropriate preparations of DDT

Immunization Control measures should not be neglected because of immunization Vaccination against cholera affords partial

immunity which lasts only three to six months It is recommended only for persons through an area where cholera is known to be present Two doses (0 5 ml and then 1 0 ml) of a reliable vaccine should be given at an interval of seven to ten days If exposure continues a stimulating dose of 1 0 ml is given every four to six months

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Brucellosis

(*Undulant Fever Malta Fever*)

Definition Brucellosis is an infectious disease due to organisms belonging to the genus Brucella the disease being transmitted to man from lower animals The acute stage is characterized by fever sweats weakness pains and aches and few or no localizing physical abnormalities Occasionally the same manifestations predominate in a chronic illness enduring for months or years

History Brucellosis constituted a febrile illness which puzzled the medical personnel of the British Army and Navy stationed in the Mediterranean area during the latter part of the nineteenth century It appeared to differ from paludism (malaria) and enteric fever (typhoid) Marston a Royal Army surgeon presented a report of his own illness in 1863 which was an accurate clinical description of brucellosis The etiological agent was described by David Bruce in 1887 Bang in Denmark reported in 1897 the recovery of another species *Brucella abortus* from aborting cattle while Traum isolated a third species *Br suis* from aborting sows in 1914 Alice Evans differentiated strains of *Br melitensis* from *Br abortus* by serological methods and predicted correctly that human disease would result from drinking raw cow's milk The classic monograph Mediterranean Malta or Undulant Fever" by Hughes appeared in 1897 Wright and Semple described the agglutination test for brucellosis in 1897 The epidemiology of brucellosis on the island of Malta was clearly defined by the brilliant reports of the Mediterranean Fever Commission issued between 1905 and 1907

Etiology At least three species of Brucella are known each of which is commonly identified with one of three animal species They are *Br melitensis* (goat) *Br suis* (hog) and *Br abortus* (cattle) Brucella are small gram negative rods which are nonmotile and do not form spores Growth is supported in liver infusion broth tryptose phosphate broth or trypticase soy broth The combined liquid solid medium of Castaneda with tryptose phosphate broth contained in a rectangular flask and tryptose phosphate agar distributed along one of the sides of the bottle affords a simple and safe method of handling Brucella cultures Primary isolation of *Br abortus* requires about a 10 per cent displacement of air by carbon dioxide Differentiation of the three species is based upon biochemical reactions serological tests and the resistance of the organisms to the bacteriostatic action of various dyes

Morbid Anatomy Brucella localizes intracellularly in the tissues of the reticuloendothelial system particularly the lymph nodes bone marrow liver and spleen The initial cellular response to the organisms is the appearance of mononuclear and epithelioid cells and then the formation of tubercles or granulomas having foreign body and Langhans types of giant cells This pattern of tissue reaction is characteristic of brucellosis but is not specific A similar type of cellular response may be encountered in some instances of sarcoidosis tuberculosis and syphilis Sometimes Brucella induces necrosis of the tissues and small abscesses may be seen in the parenchyma of the liver spleen and occasionally in the osseous tissue of the vertebrae and long bones Caseation is not a feature of brucellosis Brucella may localize in other organs or tissues such as the testicles ovaries meninges and endocardium

Epidemiology and Pathogenesis The natural reservoir of brucellosis is in domestic animals especially cattle hogs and goats In animals Brucellae tend to localize more abundantly in the mammary gland and in the pregnant uterus Healthy appearing animals may shed large numbers of organisms in the milk for months or years and the disease may provoke abortions in pregnant animals Man contracts the disease by direct contact with infected animals or contaminated secretions and excretions The organisms gain entrance through small abrasions

of the skin Human disease is also acquired through the ingestion of raw milk and fresh cheese prepared from unpasteurized milk The disease is rarely transmitted from human to human Brucellosis is primarily an occupational disease and involves rural populations much more frequently than city dwellers The disease occurs most often in farmers livestock producers meat packing plant employees and veterinarians Children are more resistant to brucellosis than are adults

In general *Br abortus* produces a milder disease than that caused by *Br suis* or *Br melitensis* Not infrequently however *Br abortus* may produce a severe even a fatal illness While the principal habitat of *Br abortus* is cattle it has been recently established that this species occurs in hogs under natural conditions The more invasive *Br melitensis* is traditionally associated with goats but in recent years naturally infected hogs have been found infected with this species in the midwestern area of the United States and an increasing number of human cases have occurred as a result of contact with infected porcine tissues Much less frequently *Br melitensis* resides in cattle *Brucella suis* is most often found in hogs but invasion of cattle has occurred Epidemics of human brucellosis have been traced to raw cows milk containing *Br suis* Except for unusual circumstances human brucellosis is a sporadic disease Because different degrees of illness are caused by the three species of Brucella it is well for physicians in any given geographic area to know what species of domestic animal is harboring the organisms and what species of Brucella is causing human disease In Minnesota and in Wisconsin most human cases are due to *Br abortus* but in Iowa *Br suis* is more commonly the cause of human disease In Mexico human brucellosis exists almost as an epidemic disease being due entirely to *Br melitensis* However in Puerto Rico *Br abortus* is the cause of human disease

Little is known about the invasive properties of Brucella The bacterial cells produce no exotoxin In common with other gram negative organisms Brucella do possess an endotoxin which participates in the pathogenesis of the illness After invasion of the tissues the organisms reside and very likely proliferate within the host s cells This intracytoplasmic parasitization may account for the chronicity of the disease both in animals and in man Hypersensitivity to Brucella antigens is an outstanding feature of brucellosis which probably contributes to the symptomatology of both the acute and chronic manifestations of the disease

Symptoms and Signs The incubation period is usually between five and twenty-one days but in an occasional patient the latent period between the entrance of Brucella into the body and the appearance of symptoms may be as long as six to nine months Brucellosis may have an abrupt onset with chills fever and sweats indistinguishable from many other febrile conditions In many instances the disease begins insidiously and it is only after days or weeks that an apprehensive patient seeks medical advice because of an ill-defined incapacitating illness An almost constant symptom of brucellosis is weakness Patients may feel reasonably comfortable while in a resting state but even the slightest physical exertion may induce extreme fatigue and exhaustion A feeling of chilliness and less often frank chills may precede a rise in temperature Profuse nocturnal sweats are a common manifestation Generalized aches and pains occur frequently and often there are headaches and pain over the thoracolumbar spine Abdominal pain may be generalized or localized to any one of the quadrants Arthralgia may occur with periarticular swelling but rarely is the tissue over the joints reddened and hot Anorexia and constipation are predominant gastrointestinal complaints though the illness may be ushered in with diarrhea A nonproductive cough may be present but symptoms referable to the upper respiratory tract are not prominent The symptomatology in brucellosis due to *Br abortus* is summarized in Table 1 Examination of the patient may reveal few or no physical abnormalities The physical findings in cases of brucellosis due to *Br abortus* are shown in Table 2 Almost one half of the patients have enlarged peripheral lymph nodes or splenomegaly Hepatomegaly is often present though jaundice is rare

As the illness extends beyond the first few days the manifestations of the disease become established in a fairly characteristic pattern Contrary to classic descriptions of the disease the temperature curve does not usually exhibit a remittent or undulating type of fever This may occur in the more chronic case or in infections due to *Br melitensis* The usual course is that of an intermittent fever with diurnal variations from 98 up to 100 to 104° F Occasionally a sustained fever may take place as observed in typhoid fever The patients may feel better in the early morning hours but

Table 1 Symptomatology in 94 cases of bacteriologically proved disease due to *Br abortus* (University of Minnesota series)

	NO OF CASES	PER CENT OF CASES
Weakness	86	91 5
Sweats	72	76 5
Chills	71	75 5
Anorexia	66	70 0
Generalized aches	65	69 0
Headache	60	63 8
Rigors	52	56 3
Nervousness	49	52 0
Backache	48	51 0
Joint pain	41	43 6
Depression	38	40 0
Insomnia	36	38 3
Pain back of neck	34	36 1
Cough	28	30 0
Abdominal pain	20	21 0
Constipation	11	11 6
Visual disturbances	11	11 6
Nausea and vomiting	9	9 6
Diarrhea	9	9 6
Genitourinary disturbances	7	7 4
Neuralgia	5	5 3

Table 2 Physical findings in 94 cases of bacteriologically proved disease due to *Br abortus* (University of Minnesota series)

	NO OF CASES	PER CENT OF CASES
Fever	92	97 9
Lymphadenopathy	43	45 7
Palpable spleen	42	44 7
Palpable liver	24	25 5
Abdominal tenderness	8	8 5
Skin lesions	8	8 5
Neurologic changes	7	7 5
Cardiac abnormalities	7	7 5
Tenderness over spine	6	6 4
Funduscopic changes	3	3 2
Orchitis	2	2 1
Pain over hip joint	2	2 1
Jaundice	1	1 0
Pain over sacroiliac joint	1	1 0

as evening draws on the face may feel flushed and a rise in temperature is associated with the onset of a headache Nights are marked by discomforting sweats and insomnia Pain involving the muscles of the back of the neck is a common complaint Persistent anorexia results in weight loss Vasomotor disturbances are reflected by the presence of an intermittent tachycardia labile blood pressure and cold and moist palms of the hands and soles of the feet Amenorrhea may appear in young women and the sexual drive in both sexes is greatly diminished Nervousness is a constant feature with the display of gross tremors of the extended fingers and tongue The patients become irritable and *mentally depressed* Visual disturbances are not uncommon Brucellosis does not cause a greater number of abortions or miscarriages in pregnancy than many other bacteremic and febrile diseases

Complications Serious complications occasionally occur and depend in part upon the species of Brucella causing the disease Organic disturbance of the *central nervous system* may be manifested by encephalitis and meningitis which are usually chronic and are frequently associated with ocular complaints and diminution in hearing *Peripheral neuritis* is not an uncommon complication especially in disease due to *Br melitensis* An excruciating type of pain over the course of the sciatic nerve either unilateral or bilateral is encountered *Radiculoneuritis* is often associated with spondylitis Destructive *bone* lesions are occasionally seen with involvement of the spine The *spondylitis* of brucellosis most often involves the thoracolumbar area and is characterized by a destruction of the intervertebral disks and the adjoining vertebral bodies Brucellosis causes a destructive suppurative *arthritis* usually attacking but a single joint A deforming and chronic polyarthritis is extremely rare if it ever does occur as a complication of brucellosis Single *osteolytic lesions of the long bones* occasionally appear similar to the Brodie s abscess caused by typhoid bacilli A more serious complication is *vegetative bacterial endocarditis Pulmonary infiltration* and *pleural effusions* have been described Though Brucellae uniformly localize in the liver in bacteremic cases with the formation of granulomas serious *hepatitis* is a rare complication However there is evidence that brucellosis may at least be a participating factor in the genesis of some cases of *cirrhosis of the liver* An occasional complication of brucellosis due to *Br melitensis* is orchitis *Cystitis* and *nephritis* have been reported as rare complications

Duration of Acute Illness In a few instances brucellosis may remain active for many years with either an intermittent or continuous state of debility In discussing the duration of infections to *Br melitensis* and summing up the experience of the Mediterranean Fever Commission Eyre stated that 85 per cent of the patients had recovered within three months Observations at the University of Minnesota Hospitals between 1937 and 1956 on cases

infected with *Br abortus* revealed that the majority of patients had recovered within three to six months and that less than 20 per cent had residuals of their disease after one year Now that highly effective therapy has become available the duration of the disease has been shortened considerably

Chronic Brucellosis Patients with chronic brucellosis must be carefully differentiated from patients with personality aberrations or neurological disorders especially if immunologic evidence points to past contact with Brucella Acute brucellosis in most patients has a marked impact upon the central nervous system and disturbs the equilibrium of the autonomic nervous system The main symptomatology of weakness headaches sweats anorexia constipation insomnia irritability nervousness and depression emphasizes the neurogenic features of the disease If active disease persists for weeks these manifestations become deeply entrenched as an emotional pattern of the patient It is readily seen why in unstable persons or in those with an underlying psychoneurosis brucellosis may have serious repercussions in the ensuing years Long after the infection has subsided a few patients flounder in a state of ill health they and their physicians explaining this lack of well being on the misconstrued basis of chronic brucellosis In endemic areas especially many persons have been exposed to brucellosis without serious consequences A considerable number have had their tissues invaded by Brucella without having had any demonstrable clinical evidence of active disease Included in this group have been those with psychoneurosis asthenia and anxiety states On the basis of inconclusive laboratory and immunological data an erroneous diagnosis of chronic brucellosis may be pinned on these emotionally disturbed people

Diagnosis The diagnosis of brucellosis can be made with certainty only on the basis of laboratory procedures Epidemiological information of a possible exposure to the disease coupled with a symptomatology consistent with brucellosis should lead the physician to make a presumptive diagnosis which then should be followed up with appropriate diagnostic procedures In a febrile patient the *leukocyte* count of the peripheral blood may be helpful in the rapid detection or elimination of brucellosis The total number of leukocytes is usually normal or reduced It is most unusual to have a count exceeding 10 000 cells per cu mm in an uncomplicated acute case The differential count usually shows a relative lymphocytosis The *erythrocyte sedimentation* rate may be normal or accelerated and is of no diagnostic value It may be of some prognostic aid when the rate is rapid in the sense that a persistently abnormal value may indicate the presence of active disease Aspirated sternal *bone marrow* may reveal the presence of granulomas which are characteristic but not specific for brucellosis

Agglutination Reaction The agglutination test provides a dependable laboratory method for making a diagnosis of brucellosis Consistent success with the agglutination reaction is dependent upon a reliable antigen and upon the techniques which are used Rapid slide agglutination tests are valuable for bedside or office use For this purpose Castaneda s antigen and techniques have been utilized at the University of Minnesota Hospitals The antigen is a formalized aqueous suspension of Brucella cells stained with methylene blue and titrated so that positive reactions are obtained only when the peripheral blood has agglutinins in a titer of 1 100 or higher as determined by the multiple dilution tube method In Castaneda s test when a drop of blood from the finger is mixed with a drop of the antigen on the slide the blue peripheral ring of agglutinated antigen may be demonstrated within thirty seconds The multiple dilution tube method should also be used In the laboratories of the University Hospitals and of the Minnesota State Department of Health a satisfactory antigen has been that supplied by the United States Bureau of Animal Industry When the agglutination test is properly performed with a sensitive antigen agglutinins are uniformly demonstrated in acute or chronic cases of brucellosis with but rare exceptions Agglutinins were observed in 267 of 268 consecutive bacteriologically proved cases of brucellosis in Minnesota Over 90 per cent of the patients exhibited titers of 1 320 or above The higher the titer of agglutinins the more likely that cultures of blood will be positive At the University Hospitals only a very rare proved case of brucellosis has failed to show agglutinins in the blood in a period of twelve years If the titer is 1 100 or above serious consideration must be given to the diagnosis of brucellosis As in typhoid fever a rising titer of agglutinins during an acute febrile illness is of considerable diagnostic importance It is the exceptional case in which a dilution under 1 100 is a reliable index of active disease Agglutinins may be demonstrated in the blood months and years after

patients have recovered from their illness Agglutinins for Brucella may be stimulated by *P tularensis* and after vaccination for cholera with *Vibrio cholerae* A technical point to be recalled is that in the macro scopic tube method a prozone phenomenon may be present in which the lower dilutions of serum show no agglutination of the antigen Rarely a blocking of the antigen antibody reaction may occur Blocking anti bodies are more likely to occur in the chronic cases

As a practical procedure there is no ad vantage in using the *complement fixation* test The *opsonocytophagic* test is a meas urement of the phagocytosis of Brucella by polymorphonuclear neutrophile leukocytes The test yields such meager and indecisive information in the sporadic cases of sus pected brucellosis that it is not advocated as a diagnostic procedure A *culture* of venous blood preferably several should be undertaken in every patient suspected of having brucellosis This applies particularly to persons having a positive agglutination reaction Bacteremia is more likely to be demonstrated in febrile patients with a high titer of Brucella agglutinins and an en larged and tender spleen At the University Hospitals positive blood cultures have been obtained in about 50 per cent of all the cases of brucellosis Most of these patients had infections due to *Br abortus* In an oc casional case Brucella may be cultured from aspirated sternal bone marrow when simultaneous cultures of venous blood re main sterile The organisms have been iso lated from the bile urine and cerebrospinal fluid

Cutaneous Tests Intradermal reactions following the injection of Brucella antigens indicate a specific state of hypersensitivity to Brucella Like the tuberculin reaction in tuberculosis a positive Brucella skin test indicates past invasion of the body by or ganisms but it does not mean that active disease is present Intradermal tests may be performed with heat killed Brucella cells a nucleoprotein fraction (brucellergin) and purified protein fraction all of which yield a delayed type of reaction reaching their maximum in twenty four to forty eight hours The carbohydrate fraction of Bru cella results in an immediate cutaneous re action The great majority of acute and chronic cases of brucellosis demonstrate positive skin tests Exceptions include the acute cases of only a few days duration and the seriously ill patients Patients with Brucella subacute bacterial endocarditis have a high titer of agglutinins and nega tive skin tests and recovery is associated with the appearance of positive skin tests Dermal hypersensitivity may persist for years after the patient has recovered from the disease It should be emphasized that all the antigens may provoke the appear ance of Brucella agglutinins in normal per sons a week or two after an injection In these circumstances titers well over 1 100 may be achieved

The skin test is an unreliable method for detecting active cases of brucellosis and its routine use is not recommended If ag glutinins are absent from the blood and blood cultures remain sterile a diagnosis of active brucellosis is not justified If in a particular case there is a history of possible exposure to the disease and the illness is consistent with the characteristic pattern of brucellosis and agglutinins are present in a titer of 1 100 or above no further informa tion is to be gained by performing a skin test If in such a case agglutinins are con sistently absent and blood cultures remain sterile a positive or negative skin test can not decide the issue

Differential Diagnosis In the differential diagnosis of acute brucellosis other febrile diseases must be considered Brucellosis is commonly mistaken for *influenza* but the latter disease is a self limited illness of short duration and may be associated with upper respiratory symptoms *Infectious mononu cleosis* is differentiated from brucellosis on the basis of hematological and serological evidence Where *malaria* and brucellosis occur together the diagnosis of the former is resolved by finding plasmodia in blood films Serological and cultural studies should differentiate brucellosis from *Hodg kins disease lymphoblastoma* and *tubercu losis Typhoid fever* is differentiated by iso lating *S typhosa* from the blood and by the agglutination test The more chronic cases of brucellosis may be differentiated only with considerable difficulty from *psycho neurosis* or an *anxiety state* Not infre quently an attack of brucellosis may be the trigger mechanism for displaying an underlying neurosis and neurotic symp toms may persist long after the infection has subsided

Prognosis The natural course of brucel losis will depend upon the geographical area where the disease is being observed and the species of Brucella causing illness In a locality where a population is malnourished and parasitized by other diseases *Br meli tensis* will cause more chronic disabling illness than in a community where good health and nutrition abound and where

brucellosis is caused by *Br abortus* In general the case mortality rate of the disease is not greater than 2 to 3 per cent and up to 75 per cent of the patients recover within three to six months Now that highly effective treatment is available the incidence of chronic illness should be considerably reduced In a small number of cases a relapsing type of febrile illness is observed Reinfections may also occur When there is repeated exposure to the disease it is not always possible to distinguish between a relapse and a reinfection

Treatment *General Management* It is of primary importance that the physician reassure any patient having either acute or chronic brucellosis that the disease is self limited and that he will completely recover from his illness Too often patients are informed that brucellosis is a chronic debilitating disease for which there is no satisfactory treatment The patient then corroborates this dismal outlook by reading about the disease and consulting with his friends and other physicians Finally he is psychologically prepared to endure an illness of several years duration It is easy to see why a mistaken diagnosis of chronic brucellosis in the place of a correct diagnosis of psychoneurosis provides an escape mechanism for many persons and a needless infliction for others It cannot be emphasized too strongly that vigorous reassurance by the physician that the patient will recover from this illness is essential whether or not specific therapy is used Another therapeutic recommendation of major value to the patient is rest physical and mental Since the outstanding symptoms of brucellosis are weakness and easy fatigability the victims are unable to pursue their *daily routines Not infrequently adequate* rest is associated with a decline in temperature and permanent recovery One need only consult the reports of the Mediterranean Fever Commission to appreciate the value of rest Any specific therapy in brucellosis should be augmented by intelligent psychotherapy There are few other diseases in which indecision or discouragement on the part of the physician is so detrimental to the welfare of the patient

Antimicrobial Therapy Treatment with antibrucella agents is recommended for either acute or chronic cases The tetracycline drugs have been used effectively in the treatment of both acute and chronic brucellosis The recommended dose for each of these drugs is 0 5 gm every six hours for three to four weeks In infections due to *Br abortus* approximately 80 to 90 per cent have recovered after an initial course of treatment Relapses can be treated favorably with a second or even a third course of chemotherapy The foregoing treatment is recommended for the mildly ill patient and especially for those having disease due to *Br abortus* For the more seriously ill patient with or without complications and particularly for those having infections caused by *Br melitensis* or *Br suis* it is recommended that tetracycline should be administered in the doses already suggested along with dihydrostreptomycin which is given intramuscularly in a dose of 2 0 gm daily The administration of the two drugs together should be prescribed for a minimum of fourteen to twenty one days Chloramphenicol is less effective than are tetracyclines

Attempts at Desensitization " It is common practice to treat the more chronic cases of brucellosis with Brucella antigens such as heat killed cells and filtrates (brucellin) Unless the injection of antigens is carefully controlled disturbing local and systemic reactions may occur Because of the dubious clinical results obtained with such a procedure and because some patients are extremely sensitive to the antigen this type of treatment has not been advocated at the University of Minnesota Hospitals It is more logical and practicable to use an antibrucella drug or drugs as an aid to the tissues in eradicating the organisms rather than subject patients to a prolonged period of desensitization or immunization with Brucella antigens

Prevention Brucellosis as a human disease will be eliminated only when the reservoir in domestic animals is eradicated *There is no entirely safe method for im*munizing human beings against brucellosis A significant segment of the population may be protected against the disease by legislation requiring that all milk destined for human consumption be pasteurized

WESLEY W SPINK

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Pasteurella Infections

PLAGUE

Definition Plague is an acute infection caused by *Pasteurella pestis* and transmitted chiefly by certain fleas Although man is very susceptible plague is basically a disease of rodents It is enzootic or epzootic in many wild rodents and in domestic rats from which it spreads to man Plague is characterized by inflammation of the lymphatic and blood vascular system and by hemorrhages in the tissues It is customary to divide the disease into three types bubonic septicemic and pneumonic The disease however may be considered fundamentally a single entity The septicemic type is characterized by wide extension and great severity The bubonic and pneumonic types have important epidemiological and clinical significance which is discussed later

History Plague constitutes the black death of history and literature (Boccaccio Pepys) Epidemics swept in waves through Europe during the Middle Ages and up to the first part of the nineteenth century often killing one in ten or more of the population In 1894 plague began to spread from western China and in fifteen years had reached most ports of the world It arrived in the United States in 1900 Small outbreaks of pneumonic plague occurred in California in 1919 and 1924

Etiology *Pasteurella pestis* (Yersin and Kitasato 1894) is a short thick bacillus with rounded ends Its form varies greatly according to the conditions in which it is obtained or grown A capsule is demonstrable This organism is aerobic grows well on usual media is nonmotile easily stained and gram negative Characteristic stained preparations show a marked bipolar configuration Under favorable conditions in darkness and moisture it may live outside the body for months or even years The bacillus is killed by thorough drying in air for two or three days It may remain viable in dead bodies for weeks in flea feces for a month and in pus or sputum for one or two weeks *Pasteurella pestis* may survive for some time in grain cotton and gunny sacks It is quickly killed by a temperature of 80 C but is very resistant to cold surviving almost indefinitely in frozen material

Distribution and Epidemiology The principal centers of human plague are China Burma and India The disease often appears in Ceylon Indo China Thailand Indonesia the eastern and southern shores of the Mediterranean the Azores and parts of Africa and South America A few cases occur from time to time in the United States a fatal instance of bubonic plague having been reported in California in 1956

Many species of wild rodent are infected with plague in various parts of the world including central and eastern Asia Russia South Africa South America Hawaii and the United States (sylvatic plague) Ground squirrels and prairie dogs have been found infected throughout the western part of the United States

Plague may be transmitted from wild rodent to domestic rat or vice versa from either of these to man and from man to man Most human infections are generally considered to be acquired from rats especially the domestic black rat which is now reappearing in Europe after an absence of over a century Human cases arise however from various other rodents as well as the black rat and from man himself Plague is usually transmitted by rodent fleas many species of which are capable of carrying the disease In man transmission is ordinarily through rubbing into the skin the infected vomitus or feces of a rodent flea In addition the human flea *Pulex irritans* is considered a potential vector and other insects have been incriminated Man sometimes acquires plague by contact with the bodies of rodents or human beings sick or dead of the disease or by handling tissues blood or discharges derived from them Apparently the disease can be acquired by ingestion Inhalation is an uncommon but extremely dangerous method of spread since it gives rise to fulminant primary plague pneumonia Usually the inhaled infective material consists of droplets from the sputum of patients with plague pneumonia

Plague is spread from place to place chiefly by migration or transportation (especially in ships) of infected rats or other rodents It is occasionally transported by patients with mild disease and by infected fleas through their survival in grain sacks

There is no evidence of any racial age or sex variation in susceptibility The development of human epidemics is determined largely by the following conditions presence of the infection in rats or other rodents size of the rodent population infestation of rodents with fleas and association of man with rodents Bad housing and bad sanitation are favorable to rats Moisture and temperatures between 50 and 80 F are generally favorable to fleas Human crowding and poor hygiene are important factors especially in droplet trans

mission which is also favored by cold temperatures

The method of transmission has great epidemiological and clinical significance Inhalation is associated with severe pulmonary disease which is rapidly fatal This form of the infection is called pneumonic plague Other forms may be grouped as bubonic plague

Morbid Anatomy Rarely a pustule is found at the site of entry of the infection The most marked changes are in and about the lymphatics and lymph nodes which are swollen edematous and hemorrhagic Buboes or swollen nodes may not be visible on the exterior The characteristic processes are edema formation hemorrhage and necrosis The spleen is much swollen grayish and soft Acute hemorrhagic nephritis and meningitis are occasionally present Inflammation of the endothelium of lymphatics and blood vessels with small embolic lesions is characteristic Large numbers of bacilli are often found in plague lesions and even in the blood Plague pneumonia though it may occur in other cases is the predominant finding in the pneumonic form of the disease in which there are usually no extensive changes in other parts of the body In this condition the lungs generally show confluent lobular consolidation but the distribution may be lobar The appearance is one of engorgement with little accumulation of fibrin or leukocytes

Pathogenesis In mild cases the bacilli remain for the most part localized in the lymphatic system with only occasional organisms entering the blood In severe cases they invade and multiply in the blood stream and may reach all parts of the body (septicemic plague) The formation of an exotoxin has not been demonstrated nor have the physiological and chemical changes produced by the infection been analyzed in detail Except in very mild or extremely severe instances a leukocytosis (usually 20 000 to 25 000 per cu mm) develops the increase being mainly in neutrophilic granulocytes There is no anemia The urine is scanty and usually contains albumin casts and erythrocytes Hematuria may occur An attack of plague usually confers immunity against subsequent infection

Symptoms The incubation period varies from two to ten days Apart from infections acquired by inhalation the severity also varies In mild cases with little extension of the disease there may be no constitutional symptoms and the patient may remain ambulant In severe infections which spread rapidly and in pneumonic plague prostration quickly occurs Headache dizziness and thirst are common complaints Many patients are confused As a rule there is high remittent fever and marked restlessness The respirations are fast and shallow *and the pulse is rapid and feeble In a few* cases a pustule may be found at the site of inoculation Signs of lymphangitis may be visible Enlarged lymph nodes or buboes begin to appear on the second day Pain in them varies from slight to severe They are usually red and tender At first they are hard but they generally suppurate and become soft and matted together Buboes may rupture and discharge their contents but sometimes they resolve without so doing The surrounding tissue is inflamed and edematous In septicemic cases blebs petechiae or purpuric spots may be seen in the skin Rarely areas of skin may become necrotic Hemorrhages may take place from the nose the stomach and the bowel and in pneumonic cases from the lungs In most so-called bubonic cases the lungs show little or nothing though patches of pneumonia may be present in such cases there is usually no sputum In pneumonic plague the physical signs are usually minimal and consist mainly of scattered fine rales but breathing is rapid and shallow and cyanosis is marked In these cases the sputum is thin at first watery and later bloody It is loaded with bacilli Although the spleen is usually enlarged in all types of plague it is often not palpable At first *apathetic patients tend to become delirious* Convulsions and coma may develop A few instances of subacute meningitis have been described The principal complications are secondary infections which often arise in buboes and in the lungs where they must be distinguished from plague pneumonia

Diagnosis The possibility of plague should be suggested by epidemiological considerations and by the clinical picture The difficulties in differential diagnosis vary with the stage and anatomical developments Plague buboes must be separated from adenitis due to streptococcal infections lymphogranuloma venereum syphilis and filariasis Septicemic plague might be confused with many forms of septicemia tularemia several forms of typhus typhoid fever and malaria Pneumonic plague should be distinguished from streptococcal pneumonia of the type sometimes associated with influenza

The specific diagnosis of plague is made by demonstrating the presence of *P pestis*

in the contents of buboes (obtained by aspiration) in blood or in sputum All material which is considered as possibly infected with plague must be handled with the greatest care All animals inoculated for diagnosis must be free of fleas and *other ectoparasites and must be kept in* insect proof cages in a room containing no other animals Everyone who handles smears cultures cages or inoculated animals must wear gowns masks and rubber gloves Throughout all diagnostic procedures *the strictest aseptic technique must* be observed

Smears should be stained with methylene blue and by Gram s method Characteristic bacilli are usually seen in good preparations of bubo contents and in pneumonic *cases in the sputum Occasionally they* are even found in blood smears Cultures and animal inoculations are often necessary however and should always be made for confirmation of smear findings The plague bacillus grows well on nutrient agar and in broth The reaction should be approximately neutral and the incubating temperature should be below 30 C Mice rats and guinea pigs are used for inoculation which is done by intraperitoneal injection or by rubbing material into the scarified skin If plague is inoculated these animals die in twenty four to seventy two hours Characteristic lesions should be found and P *pestis* should be recovered by culture Agglutination reactions cannot be used

Prognosis The course is usually run in five or six days at most In very severe cases it is over within three days The over all *fatality rate is not accurately known* because numerous mild cases are not counted Before the use of chemotherapy fatality rates in bubonic cases without wide extension of the disease ran from 25 to 75 per cent Recovery was rare in severe septicemic cases and pneumonic plague was regarded as uniformly fatal Chemotherapy greatly improves the outlook

Treatment Patients should be confined to bed and strict isolation should be maintained Good general medical and nursing care is essential The type of diet has little importance The fluid intake should be such as to ensure a daily volume of urine of at least 1500 ml Fluid including glucose solution *should be* given slowly by the intravenous route if necessary Restlessness and delirium are best treated with morphine (10 mg for adults) With the exception of antimicrobial agents other drugs have little if any place in the treatment of plague Antiplague serum and serum globulin have been recommended but their value remains uncertain and reliable preparations are not generally available

Chemotherapy Sulfadiazine streptomycin chloramphenicol and oxytetracycline have all been shown to be efficacious In one series of 118 streptomycin treated patients only 4 died A number of recoveries from pneumonic plague are on record Therapy must be adjusted to the severity of *the disease and to its duration The earlier* chemotherapy is begun the better will be the results In severe and late cases especially in pneumonic plague full dosage of the best available drug is needed The relative value of the antimicrobial agents mentioned *is not yet clear For most cases* streptomycin is recommended as the first choice It may be given intramuscularly in 0 5 gm doses at intervals of three to six hours for twenty four to forty-eight hours followed by a total daily dosage of 1 5 to 3 0 gm in divided doses for about six days in the usual case

The suggested schedule for either chloramphenicol or the tetracyclines is three treatments at three hour intervals of 0 5 gm orally and 0 5 gm intravenously followed by oral doses amounting to 4 0 gm a day for two days and 2 0 to 3 0 gm a day for four or five days The possibilities of toxic reactions to all three drugs must be borne in mind as well as the possible development of drug resistant organisms

Sulfadiazine is also efficacious in less severe cases Its use is sometimes combined with that of streptomycin In mild or very *early cases it may be* given by mouth in the initial dose of 4 0 gm followed by 1 5 to 2 0 gm every four hours until the temperature is normal After the temperature is normal *the drug should be continued* in doses of 0 5 gm every four hours for about ten days The usual precautions in the administration of sulfadiazine should be observed particularly the maintenance of an alkaline urine which generally requires the oral administration of 2 4 gm of sodium bicarbonate with each dose of sulfadiazine

Complicating infections which may develop especially in buboes or in the respiratory tract should be treated with an antimicrobial drug to which the infecting organisms are susceptible

Local Treatment Hot wet applications may decrease the discomfort of buboes Incision should not be performed unless and until suppuration is clearly present

Prevention Patients with plague should be isolated in separate screened rooms When a patient with pneumonic plague is found known and suspected contacts should be isolated and their temperatures taken twice a day for one week Attendants on patients with plague pneumonia suspected or established should wear coveralls with hoods goggles and rubber gloves All articles contaminated by the patient or his discharges should be sterilized by boiling or autoclaving or burned A room vacated by a plague patient and its contents should be thoroughly cleaned and dusted with DDT powder The bodies of those who have died of the disease must be handled with strict aseptic technique

Immunization Vaccination is considered to afford partial protection for six months but not longer It is recommended only for those who must necessarily undergo serious exposure or the possibility of serious exposure It is also used in the control of localized outbreaks of plague For individual prophylaxis two injections (0 5 and 1 0 ml respectively) of a reliable vaccine should be given with an interval of seven days If necessary stimulating doses of 1 0 ml may be given at intervals of four to six months

Rodent and Flea Control Effective prevent on of plague is achieved by adequate control of rodents especially rats The rat population should be watched for undue increases and for the presence of infected animals Rodents that may have plague should be handled and disposed of with great care and with particular attention to the possibility that they may harbor fleas In endemic areas trapping surveys are regularly made To keep down the rat population all buildings and ships should be rat proofed Adequate protection of food supplies and garbage collections against rats is essential Rat extermination campaigns should be conducted by trained personnel The rat poisons now recommended are sodium fluoroacetate and Warfarin The older poisons such as red squill and thallium sulfate may also be used All these chemicals are dangerous to man and must be used with great care Cyanide or carbon disulfide is used in fumigation but this process can be safely applied only by specially trained workers Local antirat campaigns have only brief value unless extensive rat proofing is undertaken and rat harborages are destroyed The destruction of fleas is important especially in rat harborages DDT is a very effective agent for this purpose It is applied as a powder or in solution in kerosene Control of infected wild rodents is an important unsolved problem

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TULAREMIA

(Plaguelike Disease of Rodents Deer Fly Fever Tick Fever Rabbit Fever)

Definition Tularemia is an infectious disease caused by *Pasteurella tularensis* It is destructive to wild animal populations acting as a heterogeneous infection-chain involving rodents and insects Man may enter the chain accidentally or occupationally by contaminating his hands conjunctival sac or buccal cavity with infected internal organs and body fluids of mammals birds and insects by the bite of an infected blood sucking fly or tick or by drinking contaminated domestic rural water Wild rabbits and hares have been the principal sources for the disease in man

Bacteriology *Pasteurella tularensis* is extremely polymorphous It has neither capsules nor flagella It is non motile and gram negative but stains well with fuchsin or crystal violet For routine cultures glucose cystine blood agar is excellent The guinea pig is used for laboratory tests and the mouse for testing specimens of sputum

Epidemiology Tularemia occurs in nearly all of the United States in Canada Alaska Mexico and Japan With the endemic areas in central and south Russia are apparently associated the recent geographical extensions into Norway Sweden Czechoslovakia Austria Poland and since 1946 France Belgium and Germany Seasonal occurrence with its peak in summer is associated with rabbit hunting and with the activity of the arthropod vectors Human disease may appear when 1 0 per cent of the rodents are infected More than 26 000 human cases have been observed since

1924 the highest annual incidence was 1 401 cases in 1947 Sex race and age are not factors in the incidence The history and epidemiology of tularemia have been reviewed by Ayres and Feemster and Foshay

Pasteurella tularensis requires no particular portal of entry The most important sources of human infections are (1) skinning and processing of meat and fur of wild mammals (principally cottontail and jack rabbits also muskrats beavers and pheasants) (2) arthropod bites particularly of deer flies mosquitoes and ticks or contact with their feces (*e g* in the wool of sheep) (3) ingestion of contaminated water or inadequately cooked rabbit meat (4) laboratory exposure presumably aerogenic The source of infection is not established with any degree of certainty in about half of the cases diagnosed in some regions The virulence of the invading strain seems to participate in determining the clinical form the infection takes

No proved human to human transmission of tularemia has been reported Although *P tularensis* is easily recoverable by nasal and pharyngeal swabs or from sputum in cases of tularemic pneumonia and in many without pneumonia no secondary case has ever been recorded in bedside attendants exposed to droplet infection

Morbid Anatomy The autopsy reports by Foshay Lillie and Francis stress the presence of focal areas of necrosis throughout the body Macroscopically whitish yellow foci ranging in size from hardly visible to 8 cm in diameter are found in the lymph nodes spleen liver kidneys and lungs

Symptoms The incubation period is from one to ten days Only the typhoid type proceeds as a general disease without local processes The *onset* is sudden and the patient usually remembers the hour at which he fell ill Severe headache vomiting chills and fever with an initial rise in temperature above 104 F accompanied by general aching and weakness are followed by prostration sweats and loss of weight Delirium and stupor may be present in the more severe cases The constancy of the sequence of initial rise in temperature remission and secondary rise is striking in the cryptogenic type of the disease Continuous high temperature is noted in *extreme toxemia* Ordinarily the febrile period may last ten to fifteen days in the more severe forms the disease usually runs a course of three to four weeks Febrile periods or elevation of temperature of 1 degree may persist for three weeks Papular exanthema on the palmar surfaces or roseola pustules and petechiae on any part of the body may appear at any stage in all forms of tularemia They heal by absorption or exfoliation

Enlargement of the spleen is evident in about one quarter of the cases and is not great on rare occasions it extends from three to four fingerbreadths below the costal margin Tenderness and pain indicate the existence of a perisplenitis A slight to moderate polymorphonuclear leukocytosis (12 000 to 15 000 cells per cu mm) may be noted Anemia is common The amount of urine is diminished and results of urinalysis suggest the presence of fever Myalgia arthralgia and neuralgia occur frequently

Cutaneous Tularemia Thirty six to forty eight hours after the onset of the disease with slight painful enlargement of a lymph node the patient usually notices that a previous cut or sore is inflamed and tender This primary lesion evolves from a papular to a pustular stage with a necrotic plug The pustule is supplanted by a punched out ulcer with scanty serous discharge which ultimately is replaced by a scar Not infrequently painful lymphatics with or without subcutaneous nodules (nodular lymphangitis) resembling mycotic lesions extend from the ulcer to the regional epitrocheal or axillary lymph nodes The nodes vary in size from that of an almond to that of a small orange Sometimes several groups of nodes show reactions to a single primary lesion for example the axillary and supraclavicular nodes may react to a single ulcer on the shoulder Some lymph nodes suppurate in one to twenty four months and ultimately may require incision others remain hard tender and palpable for periods up to twelve months

Ophthalmic Tularemia The primary localization is in the conjunctival sac it occurs unilaterally or rarely bilaterally Itching lacrimation photophobia and pain are early subjective symptoms which are accompanied by swelling of the pre auricular parotid submaxillary and cervical lymph nodes The eyelids are swollen and the chemotic deep red conjunctiva is studded with small discrete yellow nodules Occasionally both the palpebral and bulbar conjunctivas are covered by a gray translucent organized exudate Punched out ulcers follow the breakdown of the necrotic nodules A thin mucoid or purulent discharge accompanies the conjunctivitis for three to five weeks after which the swelling recedes and complete recovery is the rule

Suppuration of the regional lymph nodes is fairly common in ophthalmic tularemia Dacryocystitis corneal ulcers permanent impairment of vision optic atrophy and blindness have been observed following perforation of the cornea

Cryptogenic Tularemia The symptoms of a general systemic infection are fever profound toxemia with drowsiness or a typhoidal state abdominal distress and prostration Severe pulmonary symptoms in at least 50 per cent of the cases or intestinal symptoms may follow

Pleuropulmonary Tularemia The symptoms of pulmonary tularemia are variable and the diagnosis without laboratory aids is difficult The disease may begin as an inhalation infection with pulmonary symptoms or may be hematogenous secondary to some primary focus on the skin or elsewhere In the first group pulmonary symptoms less abrupt than in the pneumococcal types initiate the disease hacking nonproductive cough dyspnea fever malaise and occasional chills are present Pleuritic pains may be a dominating symptom Milder infections simulate atypical pneumonias in which the pulmonary lesions last for a month (see Primary Atypical Pneumonia p 132)

Primary tularemic pneumonia has been reported but conclusive proof that it occurs is lacking Pulmonary tularemia does develop in patients with other well recognized symptoms of tularemia such as ulcers or infections of the eye Cases of this type offer no problem in diagnosis as a rule the sickest patients are most likely to have involvement of the lungs Pleuritis usually is present and the development of a pale yellow slightly cloudy pleural effusion of high specific gravity but low cell count (2000 to 5000 per cu mm) is of great diagnostic value The pneumonic consolidation as parenchymal confluent or lobular bronchopneumonic infiltration consists of small patchy later large coalescing areas The physical signs may vary from day to day indicative of a migratory type of pneumonia usually more extensive in one lung than in the other When the process is predominantly necrotizing gangrene cavitation and pulmonic abscesses develop in the most severe cases Despite large cavities of abscesses the sputum is moderate in amount mucopurulent and rarely blood tinged or rusty Poentgenograms taken a few days to two weeks after onset may reveal a slowly advancing lobular type of consolidation The mediastinal and peribronchial lymph nodes almost always are enlarged

Oral and Abdominal Tularemia Ingestion of insufficiently cooked wild rabbit meat or water contaminated with *P tularensis* may cause a violent local process in the form of a necrotizing pharyngitis or angina abscesses on the roof of the mouth ulcers in the pharynx and nasopharynx fever enlargement of the submaxillary and anterior cervical lymph nodes and in some cases conjunctivitis Vomiting excruciating pains in the abdominal regions and diarrhea begin either during or after the fever The course may be fulminant children have had convulsions become stuporous and died in the first week of illness

Complications Symptoms of general peritonitis with the findings of plastic exudate at autopsy (Francis Fulmer) and persistent ascites requiring tapping three and five months after onset have been reported Appendicitis diarrhea and intestinal hemorrhages may be present during the last days of illness Occasionally pericarditis pneumothorax thrombosis of the veins or osteomyelitis complicates the convalescence Meningeal or leptomeningeal localization and meningoencephalitis demonstrated by isolation of *P tularensis* from the cerebrospinal fluid usually are fatal

Course and Prognosis Many of the patients are ambulatory In about one third of the cases recovery even without complications is slow it confers a relative immunity Reinfection has been reported (Green and Eigelsbach 1950) According to Foshay the mean duration of fever in untreated cases is twenty six days of the adenopathy three to four months and of the disease five and one half months Even though clinical recovery is evident *P tularensis* because of its facultative intracellular parasitism may remain alive in the tissue for months perhaps years (Blackford Foshay and Mayer) Pulmonary tularemia has had a high fatality rate (62 5 per cent) the typhoidal cryptogenic form has had a lower one (19 per cent) when treated with antimicrobial agents (Giddens *et al* 1957) The average mortality rate for tularemia in the United States has been reported at 5 6 per cent In Louisiana the rate dropped from 33 per cent in 1934 to 7 5 per cent in 1948 because of the use of streptomycin

Diagnosis Tularemia should be considered in every doubtful case of fever or atypical pneumonia in which the patient may have been exposed by contact with some animal The following immunological and bacteriological tests in the order mentioned are valuable diagnostic aids

1 *Intracutaneous or percutaneous allergic skin tests* with detoxified formalin killed *P tularensis* as antigen (Foshay) may yield positive reactions on the third day of illness Since hypersensitiveness of the skin is a notable feature of tularemia throughout the disease this method deserves more frequent use than has been customary in the past The inflammatory response is similar to the reaction of tuberculin and the wheal attains maximal size forty eight hours after injection or application on the scarified skin

2 *Agglutination and Complement Fixation Tests* Specific antibodies in the blood never appear before the tenth or twelfth day of the disease and thus the agglutination test is of little help during the first period of the disease when it is most difficult to diagnose clinically The serum of patients with brucellosis furthermore may give positive reactions with tularemic antigens When repeatedly applied in order to determine a rise in the titer of the agglutinins the test is valuable and irreplaceable for retrospective diagnosis

3 *Cultures* on glucose-cysteine blood agar or thioglycolate blood agar inoculation of guinea pigs or chick embryos with blood pleural effusions and infected material or of mice with sputum during life and with blood from the heart at autopsy should be made when agglutinins are absent and the course of the disease suggests tularemia *Pasteurella tularensis* may be isolated from the sputum of persons suffering from tularemia who manifest no frank clinical signs of pulmonary involvement The danger to the laboratory worker who makes cultures or animal tests should be guarded against

Differential Diagnosis Tularemia may masquerade in a variety of forms the signs and symptoms are so similar to many other acute infectious diseases notably influenza psittacosis atypical pneumonia undulant fever typhoid and septicemia that differential diagnosis is difficult The subcutaneous nodules and the enlarged lymph nodes have been erroneously attributed to sporotrichosis and at autopsy tularemia has been mistaken for tuberculosis In any locality where the infection is prevalent among rodents the clinician must have tularemia in mind

Treatment Streptomycin and dihydrostreptomycin are rapidly curative Higher doses (2 0 to 4 0 gm a day) are necessary in the severe typhoidal or pleuropulmonary form than in the milder ulceroglandular or ophthalmic form (0 5 to 1 0 gm) The effect of the drugs is most dramatic in acutely ill patients treated early in whom the disease is pursuing a stormy course The broad spectrum antimicrobials are also effective but less so than streptomycin The tetracyclines or chloramphenicol given orally in an initial dose of 25 mg per kg of body weight followed by doses of 0 5 to 0 75 gm every six to eight hours have been recommended The appearance of drug resistant mutants of *P tularense* in human beings has not been recorded and any of the drugs is effective in controlling relapses As a rule no benefit is derived from antimicrobial therapy for longer than ten to twelve days The local cutaneous lesions should not be incised they are best treated by hot moist applications containing some germicide which makes the handling of the dressings less dangerous Suppurating lymph nodes should be incised only after they show definite fluctuations Since febrile reactions and even chills may follow such a procedure surgical treatment of tularemia should be judicious

Prevention Tularemia as an everlasting enzootic and frequently epizootic disease of rodents and with a latent parasitism in insects cannot be eradicated There is a likelihood that an effective immunizing antigen may be prepared Until the prophylactic value of vaccine has been established it is imperative that sportsmen butchers and those who live in regions where the infection prevails should be educated to the dangers of this disease Rubber gloves should be worn while dressing wild rabbits Laboratory workers should use face masks To render the meat of rabbits harmless thorough cooking is imperative Some reduction in the incidence of tularemia would be accomplished by supervision of interstate shipments of wild hares and of their sale for food in markets and restaurants

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Glanders

(*Farcy Morve Rotz Malleus Hautwurm*)

Definition Glanders an acute infectious disease of horses mules and donkeys occasionally transmitted to man through discharges from the skin eyes respiratory or digestive tract is caused by *Malleomyces mallei* It is characterized by nodules in the internal organs and by ulcerative papules or nodes of the skin and subcutaneous tissues and of the respiratory mucous membrane

Epidemiology Suppressive measures have almost freed the United States and Canada from equine glanders since 1936 only twelve cases have been reported from the United States It is seen in grooms coachmen veterinarians soldiers farmers and the like Several cases in laboratory workers and instances of human to human transmission have been reported

Etiology In smears prepared from the viscid pus of the abscesses *Malleomyces mallei* is seen usually in small numbers within and between cells as a straight or slightly curved rod 1 5 to 5 0 μ long and 0 5 to 0 8 μ broad singly sometimes in pairs or parallel bundles It is nonmotile noncapsulated gram negative and stains distinctly with alkaline methylene blue or carbolthionin exhibiting a characteristic beaded granular or bipolar appearance Cultivation may be difficult because the organism adapts itself slowly to artificial media Virulence for different animals is variable The hamster is the most susceptible but for diagnostic tests the guinea pig is most suitable After intraperitoneal or even subcutaneous injection *Malleomyces mallei* localizes in the serosa covering the tunica vaginalis and incites a purulent exudate and swelling of the testes by the second to twelfth days This testicular reaction first described by I Strauss in 1889 is diagnostically significant provided that the exudate is examined both microscopically and culturally

Clinical Manifestations *Acute Glanders After the usual incubation time of three* to five days there are general malaise headache anorexia chills temperature up to 104 F vomiting and myalgia There are local swelling and infiltration at the site of the cutaneous infection ulcers with irregular edges and sloughing and multiple intramuscular and subcutaneous nodules along the lymphatics—the so called farcy buds" which gradually transform into abscesses They show little tendency to heal When the primary lesions are in the nose the sticky blood tinged secretions become ropy and this material excoriates the skin and mucous membrane of the mouth tonsils throat larynx and trachea over which it runs General infection accompanied by an exanthematous eruption delirium and coma may lead to fatal termination in two to three weeks owing to circulatory collapse Few patients recover from acute glanders

Chronic Glanders Negligible constitutional symptoms without fever may begin first general malaise and pains in the extremities are common Within one to four weeks irregular fever tends to assume a septic character Subcutaneous or intramuscular abscesses appear on the upper and lower extremities When the infection localizes in the periarticular tissues the joints may be involved Partial healing and apparent quiescence may be followed by recurrence of symptoms abscess formation pulmonary consolidation pleural disturbances and emaciation This peculiar remittent disease may drag on for years The lesions may heal slowly or a remission with rapid generalization may be fatal Many patients succumb to cachexia and amyloid disease Chronic glanders may be latent throughout its entire course An estimated 30 to 50 per cent of the patients survive chronic glanders without treatment

Diagnosis The clinical picture is not pathognomonic Any wound infection in a person who has been in contact with horses or with a laboratory handling *Malleomyces mallei* should be regarded as gravely suspicious and culture and inoculation of hamsters should be instituted

Complement fixation and agglutination tests in acute glanders and the diagnostic intradermal test with commercial mallein (0 1 ml of a 1 100 000 dilution) are indispensable in chronic glanders

Treatment The patient must be isolated and the discharges carefully disinfected with hypochlorite or benzalkonium chloride (Roccal) Aside from symptomatic treatment chemotherapy with sulfonamides penicillin or streptomycin in the few patients treated has yielded promising results

MELIOIDOSIS

Until quite recently a rare specific glanders like infection melioidosis—as a rule with a septicemic course caused by *Malleomyces pseudomallei* (*Pfeifferella whitmori*)—was believed to be confined to southeast Asia Guam and Madagascar But two cases of chronic melioidosis have

been discovered in persons known never to have been outside the Western Hemisphere Human to human transmission is unknown Rats are suspected primary reservoirs but guinea pigs cats dogs pigs cattle goats and sheep have been found infected According to Chambon isolation of the organism from soil and mud from marshes and ricefields in Cambodia and Vietnam probably explains the epidemiology of human melioidosis more adequately than does ingestion of food contaminated with infected rat excreta Morphologically in stained preparations *Malleomyces pseudomallei* resembles the organism causing glanders and produces a Strauss reaction but it is actively motile liquefies gelatin forms corrugated colonies attacks a wider range of carbohydrates and is as a rule highly virulent for laboratory animals and serologically distinct from *Malleomyces mallei* The inexperienced may confuse it with *Pseudomonas aeruginosa* The disease has developed as an acute pulmonary infection followed by hematogenous dissemination to several viscera miliary abscesses septicemia and death within a few days Only 10 per cent of the cases have been diagnosed during the patient s life Patients from endemic regions who have recovered from the acute phase may be discovered in the Western Hemisphere with febrile suppurations in diverse localizations Isolation of the organism leads to the diagnosis of the illness known to extend its course interrupted by afebrile periods and without constitutional symptoms for up to eight years Intensive chemotherapy with sulfonamides and penicillin in very large doses has in a few cases favorably influenced its course

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Anthrax

(*Charbon Maladie Charbonneuse Milbrand Malignant Pustule or Cutaneous Anthrax Woolsorters Disease Rag Pickers Disease or Pulmonary Anthrax*)

Definition Anthrax an acute infection caused by *Bacillus anthracis* attacks many species of animals in particular herbivora and is transmissible from them to man Clinically it may be an external (malignant pustule and malignant edema) or internal (pulmonary and rarely intestinal) disease

History Anthrax has been known from antiquity the name is derived from the Latin *anthrax* a carbuncle Maret (1752) and Fournier (1768) defined the clinical malignant pustule in man Chabert (1780) described anthrax in animals and Barthelémy (1823) proved its transmissibility by inoculation Subsequently Davine (1863–1864) showed that anthrax is caused by a living organism that multiplies in the body invades the blood stream and produces death by septicemia He found the same organism in the malignant pustule establishin the etiology of the disease in man and animals Final proof of the causative role of *Bacillus anthracis* was furnished when R Koch (1877) described the formation of spores cultivation of the organism *in vitro* reproduction of the disease by injection of pure cultures and recovery of the bacillus at autopsy The study of anthrax established for the first time the specific relationship of a microbe to an infectious disease

Etiology *Bacillus anthracis* so designated by Ferdinand Cohn (1875) and by many claimed as the cornerstone in modern bacteriology is a nonmotile gram positive rod which forms capsules in the tissues of man and animals Under conditions of unfavorable growth outside the body it forms ellipsoid or oval spores quite resistant to heat (ten minutes boiling) and to chemical disinfectants The chief criteria for identification of *B anthracis* virulent for mice or guinea pigs and for its differentiation from *B cereus* are lack of motility inability to ferment salicin feeble hemolysis reduction of methylene blue peptonization of milk failure to multiply at 45 C or on agar containing 10 units of penicillin per ml formation of smooth mucoid colonies containing capsulated bacilli grown on sealed plates of bicarbonate medium and susceptibility to specific phage action (Burdon 1956) The capsular antigens consisting of polyglutamic acids are aggressins In combination with soluble somatic polysaccharide they incite protection and protective antibodies An extracellular toxin produced *in vivo* and *in vitro* causes edema

secondary shock and death in the experimental host a syndrome identical with that in natural anthrax (Smith and others 1955) Apparently no conventional antigen antibody protection is involved in acquired resistance to anthrax

Epidemiology Man contracts anthrax through direct or indirect exposure to animals or animal products rarely is it spread from animal to animal Infection occurs primarily or secondarily from feeding on contaminated pasture in low lying marshy areas or on artificial foodstuffs such as bone blood fish and maize meal In 1951 raw bone meal imported through Belgium from Asia and southern Europe was responsible for numerous outbreaks of anthrax in swine Sun-dried bone has caused at least twenty cases of anthrax in man in England Anthrax spores have been found widely distributed throughout a factory using goat hair in the manufacture of interlining for men s coats But despite recovery of virulent *B anthracis* from air samples and dust collected from machinery walls floors clothing and body surface of workers pulmonary anthrax is rare A relatively high but variable natural resistance is probably responsible for the low annual incidence despite probable widespread dissemination of spores in factories handling infected hair or wool

Anthrax infection exists in a few fairly well defined districts in the United States (1) southeastern South Dakota northeastern Nebraska southern California and New York (2) the delta regions of the lower Mississippi Valley with extensions downstream from areas with favorable neutral or alkaline soil (Stein and Van Ness 1956) and (3) a belt along the Texas gulf coast Occasional serious outbreaks occur but the incidence is kept down by preventive measures The disease causes major epizootics throughout the world particularly in Asia Africa and southern Europe

Anthrax in man may be divided into two epidemiological groups agricultural and industrial *Agricultural anthrax* is usually acquired while handling skinning or autopsying infected animals Farmers butchers sheep herders and veterinarians are the usual victims The death rate unfortunately continues high because diagnosis and treatment are delayed The lesion takes the form of a malignant pustule *Industrial anthrax* arises from handling wool or animal hair hides or skins and may take the form of cutaneous or pulmonary anthrax It has recently increased in New England and the Middle Atlantic states owing to the handling of imported infected hair wool carpet wool and goat hair and skins from Asia and North Africa where organization of the livestock industry is primitive (Wolff and Heimann 1951 Steele)

Over 95 per cent of the cases of human anthrax in the United States are cutaneous These have been caused by contact with horsehair shaving brushes with anthrax meningitis as a frequent complication Pulmonary infection was commoner than malignant pustule fifty years ago but thanks to improvements in industrial hygiene legislation and the introduction of exhaust ventilation dust masks and proper clothing this type is now infrequent

From 1944 to 1957 (first six months) 611 cases of human anthrax occurred in the United States The highest incidence was in 1947 with 69 cases 75 per cent in seven northeastern states where industrial exposure is the usual source of infection In the remaining forty-one states agricultural exposure involved farmers and veterinarians There are no recent records of human anthrax caused by ingestion of contaminated milk or meat In one series of 117 cases observed between 1933 and 1955 only one pulmonary infection was diagnosed (Gold 1955) The loss due to animal anthrax during 1951–1953 in 2 360 outbreaks has been estimated at 2 988 cattle 314 sheep 670 horses and mules 13 deer 860 mink and 2 dogs

The infection chain animal man is as a rule broken In 1948 however a man to man transmission was proved (Reilly and Beeson) Healthy persons may carry spores in their clothing

Symptomatology *External Anthrax* MALIGNANT PUSTULE The most common form (95 per cent) of cutaneous anthrax is seen by the physician when the carbuncle has already developed From one to three days after infection a reddened area of the skin on the arm neck or face shows a fleabite like patch transformed into a painless and insensible papule Intense itching accompanies this primary lesion in its progress to a vesicle with a hard dark purplish black center Interestingly the site of the lesions varies with the nature of the industry Hide porters are frequently infected on the back of the neck which is more open than other parts to excoriation In butchers and veterinarians who handle carcasses the arms or hands are affected As a rule there is only one focus but scratching may lead to autoinfection and formation of several papules and vesicles with yellowish or hemorrhagic or even puru

lent content Within a few hours after the papules appear adjacent soft tissues become infiltrated and swollen Coagulation necrosis desiccation or scratching produces a dark bluish red tough leathery eschar which extends both in depth and width and forms with the densely edematous ring *studded with small vesicles the characteristic carbuncle* The term "pustule" is unfortunate for pus does not form Massive infiltration joins extensive hemorrhagic edema which may extend along the neck to the face or chest or even to the abdomen and lead to extraordinary distortion of the involved parts Reddened lymphatics spread from the carbuncle to the regional lymph nodes which are painful swollen and sometimes covered by an area of reddened and inflamed skin In the mildest form with but little swelling the primary papule vesiculates rapidly and the resulting scab separates in a few days Recovery in more severe cases is indicated by the gradually sloughing suppuration of the eschar at the end of the first week recession of the edema and slow healing of the extensive defect by granulation leaving a disfiguring scar

Quite early headache joint pains nausea malaise and fever may accompany development of the carbuncle The temperature varies in most cases it is elevated but it may be normal or even subnormal The leukocyte count may show a slight increase (10 000 to 13 000 cells per cu mm) or leukopenia with 60 to 85 per cent polymorphonuclear leukocytes Despite the alarming aspect of the carbuncle the general manifestations of illness may be exceedingly slight On the other hand even the early stages of the local process may be accompanied by profound malaise vomiting circulatory collapse cyanosis profuse perspiration diarrhea and subnormal temperatures Death may take place in three to five days Blood cultures usually reveal anthrax bacilli

The presence of bacilli in the blood stream does not always constitute an unfavorable prognosis In fact the mode of action of the anthrax bacilli is by no means clearly understood The invasion in the blood stream occurs late remains confined to the blood vessels of the liver lung spleen and kidney and is accompanied by severe toxic manifestations Embolic bacillary occlusions of the capillaries and the formation of poisons in the extravasations of blood into the organs may be principally responsible for the severe symptoms and deaths According to Szendey cerebral hemorrhage is present in at least 40 per cent of the fatal cases Cyanosis and respiratory distress are always grave symptoms

MALIGNANT ANTHRAX EDEMA This is observed in the loose connective tissue of the eyelid hand neck thigh and mucous membranes It is characterized by a doughy soft transparent faintly reddish or anemic *infiltration and swelling without papules* and vesicles following rather than preceding constitutional symptoms Rarely circumscribed it spreads rapidly and is apt to terminate in extensive sloughing and gangrene In general the outcome of the edematous form is less favorable than that of the carbuncle

Internal Anthrax PULMONARY ANTHRAX This presents no characteristic clinical symptoms The onset is sudden with rigor and fever slight or excessive Aside from general malaise headache and circulatory disturbance the patients may complain of a feeling of tightness in the chest and difficulty in breathing which in some may be accelerated to 40 to 50 respirations a minute The sensorium is usually clear The auscultating signs are usually those of bronchitis The mucosa of the nose larynx and pharynx becomes reddened and swollen With increasing dyspnea cough and pain in the chest pneumonic infiltrations or even pleuritic exudates become discernible Anthrax bacilli may be demonstrated in the frothy occasionally blood tinged sputum Death may occur within eighteen to forty-eight hours when the disease lasts longer (up to ten days) delirium and unconsciousness govern the clinical picture On the other hand absence of the severe symptoms usually accompanying acute infections and the rapidity with which collapse sets in are characteristic of this form The disease is often suspected because the patient s occupation subjects him to inhalation of dust from hairs soiled with spores

GASTROINTESTINAL ANTHRAX This form rare in the United States but frequent in Indonesia and southeast Asia may result from ingestion of infected food or may follow the external type when the organisms are carried to the mouth from external lesions it may be secondary to anthrax elsewhere in the body It may be symptomless as in Sinai s 38 patients who had eaten inadequately cooked meat from an infected calf Or as in Soloweiff s thirty cases traced to infected sausage the symptoms may include persistent vomiting constipation and rarely diarrhea an almost empty gastrointestinal tract with the occasional discharge of blood tinged fecal material or pure blood

abdominal distention and tenderness peritonitis and accumulation of exudates and relatively little fever (maximal elevation 102 2° F) His patients were restless anxiety ridden and much concerned about their illness Collapse cyanosis and apoplectic death terminated most infections within one to three days one patient died in eleven days At autopsy localized phlegmonous hemorrhagic infiltrations and carbuncles were noted in the ileum and cecum and hemorrhages in the myocardium and brain

Diagnosis The diagnosis is greatly facilitated when the cutaneous lesions are characteristic and when the anamnesis and occupation of the patient suggest this infection If no information is available differential diagnosis between anthrax carbuncle and simple coccal infections requires laboratory assistance Any physician with a microscope of medium power and certain staining reagents can make an early diagnosis and thus reduce the risks If a vesicle has formed films are made from the serum and stained If it is already broken gentle scraping of the pimple or puncture of the eschar will produce serum rich in typical encapsulated bacilli when stained with a polychrome eosin methylene blue stain (Wright or Giemsa) Their direct cultivation on peptone agar should always be attempted If the specimen has to be shipped the tissue serum should be dried on silk threads or a sterile glass slide On occasion both the smear and the culture may show few or no anthrax bacilli while cocci may grow in the culture Repeated examinations and cultures are therefore indicated In view of the occurrence of anthrax like bacilli on the skin it is imperative that diagnoses be confirmed by animal inoculations preferably in guinea pigs or mice In pulmonary anthrax the bacillus has been found microscopically in the sputum and in the pleural exudate Vomitus should be inspected when gastrointestinal anthrax is suspected

Terminally and sometimes when severe general symptoms are present the bacillus may be cultivated from blood if not less than 20 ml are taken Even in nonfatal cases and in the absence of symptoms indicative of generalization the anthrax bacillus may be isolated from the blood Blood or cerebrospinal fluid after it has been treated with 3 per cent acetic acid solution may be centrifuged and the sediment stained with Wright s stain and examined for bacilli

Prognosis The prognosis in external cutaneous anthrax is favorable provided the pustule is not on the neck or face and has not been irritated by physical and chemical procedures Moreover if the nature of the pustule is correctly and promptly diagnosed the patient placed in bed and specific treatment instituted not later than the third day the chances for recovery in most infections are favorable To be sure the statistics amply attest to the uneventful recovery without complications or sequelae without specific treatment Individual susceptibility to anthrax varies considerably cutaneous even visceral infections are not as deadly as popular belief would indicate Thompson reports that only one of twenty veterinarians (18 with *malignant pustule* one throat infection and one generalized



FIG 26 Cutaneous anthrax with facial and orbital edema immediately preceding oxytetracycline therapy Innumerable *B anthracis* visible on stained smear of material from lesion (Courtesy of Drs Vernon Knight and A Ruiz Sanchez)



FIG 27 Same patient as in Figure 26 seventy two hour after start of oxytetracycline therapy Note virtually complete disappearance of edema *B anthracis* no longer demonstrable in stained smears of exudate (Courtesy of Drs Vernon Knight and A Ruiz Sanchez)

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symptoms in the hand (2) a diffuse generalized skin eruption with arthritic and constitutional symptoms and negative blood culture and (3) septicemia with or without cutaneous lesions The reddish blue swelling with raised edges well demarcated or slowly advancing and a sensation of tightness with burning or itching pain in the inflamed area are characteristic appearing one to seven days after injury Stiffness and pain in the interphalangeal joints are common In the rare generalized form purpuric eruptions develop remote from the primary portal of infection The diagnosis offers no difficulties in view of the history and absence of fever it can be confirmed by culture of biopsy material Penicillin is the drug of choice for treatment

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Mycobacterial Infections

TUBERCULOSIS

Definition Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* The disease is widespread among men and animals uniformly fatal in some species seldom if ever in others acute and generalized in some persons chronic and localized in others Pathologically the disease is characterized by inflammatory infiltrations tubercles caseous necrosis abscesses fibrosis and calcification

History Archeological discovery of skeletons bearing the marks of tuberculous lesions indicate that the disease was present in remote antiquity In the earliest medical records it was called consumption or phthisis because of its most conspicuous external feature wasting Long considered to be of many varieties and origins the unity of the disease was first recognized by Laennec The correctness of his conceptions was not universally acknowledged until Koch in 1882 isolated the specific organism and reproduced the disease experimentally The avian form of bacillus was isolated in 1890 by Mafucci and the bovine form in 1898 by Theobald Smith Within a few years after 1895 when Roentgen announced his discovery the adaptation of roentgenography to the study of anatomical changes caused by tuberculosis added an understanding of the disease which today is indispensable in clinical practice Finally in 1944 the discovery by Waksman and his co workers of a practical and highly specific antibiotic led the way in a new attack against the disease the success of which has far exceeded anything previously attempted or done

Distribution Under certain conditions fish reptiles amphibians fowls and mammals may acquire tuberculosis although in their wild state these classes are not very susceptible Animals in captivity sometimes fall easy prey to the disease Among domesticated animals it occurs in cattle swine and gallinaceous birds and is seldom observed in dogs horses and goats In the United States and some other countries an active plan of eradication of tuberculosis from cattle has been highly successful in still others the prevalence of infection among bovine herds is estimated to be as high as 40 per cent

Incidence in Man No branch of the human race has escaped the touch of tuberculosis The severity of its effects however varies greatly in different communities Although the infection is common most people survive The occurrence of infection mortality and morbidity therefore must be analyzed separately Formerly in most communities almost all adults reacted to the tuberculin test and this is still true in some sections With few exceptions the results of tuberculin testing provide a reliable measure of the existence and rate of occurrence of tuberculous infection in populations On the basis of such information the National Tuberculosis Association in 1957 estimated that approximately 55 000 000 people in the United States had already been infected Similar evidence however indicates that the time of infection is being progressively postponed to the ages beyond adolescence Tuberculin testing (patch test) of children aged thirteen to fifteen years in secondary schools of New York City in 1956 revealed only 6 9 per cent of 54 373 to be positive reactors Among large groups of recruits of the United States Navy aged seventeen through twenty years 4 6 per cent in 1954 were reported to have reacted to the Mantoux tuberculin test Usually in communities with relatively high rates of death from tuberculosis the rate of infection among youths is also relatively high In Paris in 1952–1953 50 per cent of the children aged fourteen were estimated to be infected (Lotte) in *Japan in 1953* the percentage of reactors in this age group was 65 to 80 (Japan Anti Tuberculosis Association) Most surveys indicate that the rate of infection is greater among males especially after the age of adolescence this is thought to be due to their wider peregrinations leading to more frequent contacts with sources of infection

infection) died The general fatality rate is around 20 per cent (Holland and the United States) but may be as high as 40 per cent There is generally a low fatality rate for tannery anthrax but a high rate for that resulting from animal contact Septicemia with and without involvement of the viscera and sometimes meningitis are serious complications Double and multiple infections occur at times and recurrences are possible though not usual When the eruption assumes the form of anthrax edema indications of diminished resistance are obvious and the outcome may be in doubt In respiratory and alimentary anthrax the prognosis is grave largely because of the extensive visceral destruction and the presence of bacteremia (up to 300 to 400 bacilli per ml) The presence of bacilli in the blood culture justifies an unfavorable prognosis although dramatic cures may be achieved by modern therapeutic procedures The true nature of mild cases may occasionally be suspected but is rarely proved An attack of the disease if it produces immunity induces a resistance of only short duration Second attacks of cutaneous anthrax have occurred within a year

The average hospital stay is about two weeks and provided the ulcer heals in two weeks the patient returns to work within five to six weeks

Treatment The drug of choice is penicillin in daily doses of from 100 000 to 600 000 units for two to seven days The excellent clinical response to broad spectrum antimicrobial drugs is lower and positive cultures are obtainable longer than when treatment with penicillin is instituted as soon as anthrax is diagnosed Local edema and erythema disappear within twenty four to forty-eight hours pain and tenderness of the lymph nodes and all signs of systemic reaction subside rather promptly The advantages of oral administration make the tetracycline compounds particularly useful in the treatment of ambulatory patients European clinicians recommend combined serum penicillin therapy in grave internal anthrax

Prevention Prevention of the infection in man must first be directed to its suppression in animals by veterinary control measures The proposals by the U S Public Health Service include annual vaccination of animals with a standardized potent spore vaccine or the recently developed alum precipitated protective antigen This also prevents the disease from being a major agricultural economic problem Sterilization of contaminated bone meal readily accomplished is part of federal and other public health control programs Tanneries and processing plants for animal hair and wool have tried diverse methods of sterilization but have found procedures effective in eradicating the anthrax spores from contaminated animal hides and hair unacceptable Heating or chemical sterilization alter the physical properties of the products and render them valueless Workers in tanneries and wool factories may be protected by rubber gloves and aprons and proper ventilation to carry off the infective dust Ultimately prevention in some cases becomes a problem of active immunization The Pasteurian living attenuated spore vaccine was never applicable to man and heat killed vaccines have afforded inadequate protection Wright has grown a nonproteolytic mutant in a chemically defined non protein medium and has developed a sterile nontoxic product which effectively immunizes test animals This antigen has been used on employees of woolen mills in Pennsylvania and in England but reports on its effectiveness are not yet available

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Erysipeloid of Rosenbach

Since characterization of swine erysipelas and isolation of its causative agent *Erysipelothrix rhusiopathiae* in the United States in 1921 attention has been called to human infections Essentially an infector of swine and poultry the organism is widely distributed in nature on putrefying animal and vegetable matter and on the slime of fish during the warm weather Only a few human infections are attributable to contact with animals most are occupational and are due to abrasion of the skin among fish workers slaughtermen butchers cooks and housewives Three clinical forms have been described (1) a mild localized skin eruption accompanied by mild arthritic

studied the chemistry of the bacillus which is made up mainly of lipids waxes poly saccharides and proteins There is no cap sule Though the organism is tenacious of life and may survive many months in the dark or when refrigerated it does not live long when exposed in rooms well supplied with unfiltered daylight (C R Smith) and it is killed by boiling in water for two minutes or pasteurization at 60 C

Resistance Man is relatively resistant to tuberculosis Infection is common but less than 10 per cent of all those infected die of the disease This bespeaks a native re sistance which as a rule is highly effective Its precise nature is not understood and it cannot be clearly distinguished from the numerous other factors which influence the course of the infection Natural resistance varies with age Young infants may go on to acquire generalized tuberculosis soon after the first infection and the case fatality rate at this time of life is relatively high The mortality rate is generally low between the age of five and adolescence when there is a rise reaching its peak in females in the early twenties and somewhat later in males This suggests strongly that biological influences associated with puberty alter natural resistance The relatively high death rate in old men as compared with old women may involve similar forces

Allergy and Immunity These factors which begin to assert themselves shortly after the development of the first lesion modify subsequent reactions Koch demon strated that a guinea pig infected with tuber cle bacilli slowly suffers an indolent and sometimes ulcerating lesion at the site of inoculation and dies with progressive and generalized tuberculosis after a lapse of several months Within a few weeks after the inoculation the tissues for the first time become sensitive to tuberculin This altered reaction is known as tissue hypersensitivity a form of allergy Similarly Koch found that a second inoculation of bacilli into the skin of a previously infected animal pro duces a lesion which behaves differently from the primary The local reaction is rapid and intense with a tendency to ab scess formation ulceration extrusion of the necrotic matter and subsequent healing Dissemination of bacilli from this focus through the lymph and blood streams is much slower and less severe This the *Koch phenomenon* is a manifestation of allergy and of acquired relative immunity the nature of which has been identified only partly Weakly concentrated humoral anti bodies may be demonstrated More impor tant however as shown by Lurie is the accelerated mobilization of phagocytic cells at the site of infection these may form an effective barrier against further invasion If the primary infection was not overwhelm ing or was accomplished with an attenuated strain of bacilli the animal now may sur vive the effects of reinfection for many months In the human being tissue hyper sensitivity which usually develops within five or six weeks after the first infection helps to explain certain intense inflam matory reactions such as serous pleurisy Acquired immunity which is never abso lute seems to develop much more slowly and in man may not reach its height for a year or more Allergy as indicated by the intensity of the reaction to tuberculin is not a measure of immunity but most workers believe that the two are closely associated

Heredity The superior resistance of cer tain groups such as Jewish people from certain geographical areas suggests that hundreds of years of experience with tuber culosis results in the elimination of the susceptible and the survival of relatively resistant members It has been intimated that specific immunity may be inherited to a degree but this has never been proved The evidence is more suggestive that some racial stocks have a stronger or weaker natural resistance—a genetic character

Constitution and Race Clinicians have often described types of people thought to be susceptible to tuberculosis *e g* the asthenic thin skinned silken haired titian blond However precise identification of the nature of constitutional factors remains for the future Kallmann and Reisner studying monozygotic and dizygotic pairs of twins found that the chance of developing tuber culosis increases in direct proportion to the degree of genetic relationship to a tubercu lous person Lurie has been able to breed families of rabbits in which the greatly varying resistance is a function of their genetic constitution The higher mortality among Negroes in many parts of the world is attributed in some degree to poor living conditions However the striking tendency of the lesions to undergo caseation rapidly and the frequency of generalized dissemina tion of the infection indicate that there is a real constitutional peculiarity in this race In the United States the tuberculosis death rate for nonwhite persons is about three times that among white people in 1910 11 per cent of all deaths from tuberculosis occurred in nonwhite people while in 1954 the proportion was 26 per cent The disease

Medlar in 1947 after an extensive study of necropsy material in New York City reported that evidence of tuberculous infection was present in approximately 35 per cent of persons ten to nineteen years old at the time of death The incidence of infection rose to about 65 per cent in the thirty to thirty nine years age group and to 85 per cent or more in the group above the age of sixty years His comparative study of 17 196 necropsy protocols led him to conclude that the incidence of tuberculous lesions was approximately the same in 1940 to 1945 as it was in 1916 to 1920 in striking contrast to the steady diminution of deaths due directly to the disease It may be inferred therefore that infection is still widely prevalent but that the infected persons better resist the invasive effects of the resulting lesions The increase of relatively resistant persons is presumably a result of the improvement in living conditions nutrition and other hygienic standards

Mortality from tuberculosis also varies greatly in different localities It is estimated that it causes several million deaths in the world each year Areas with high rates include eastern Europe Asia Latin America Alaska Greenland Newfoundland and Labrador Differences in the number of deaths from the disease per 100 000 population are exemplified by the following experiences reported for the year 1956 Chile 63 1 Finland 38 1 France 28 6 Switzerland 18 4 England and Wales 12 Sweden 9 8 Canada 7 8 Israel 6 1 Netherlands 5 4 * For many decades the rates in many nations have declined steadily exceptions being noted in temporary upward trends during great wars The decline was sharply accelerated about 1947–1948 when specific chemotherapy became available

In the United States the rate per 100 000 per year declined from 202 in 1900 to 113 1 in 1920 45 8 in 1940 and to 8 3 (provisional) in 1956 The most striking reductions have occurred in the early decades of life (Fig 28) In this country tuberculosis now stands thirteenth among the leading causes of death in 1956 it was responsible for one in every 113 deaths compared with one in 43 in 1950 Death is due to the pulmonary form of the disease in about 92 per cent of all cases and to nonpulmonary or generalized forms in 8 per cent In 1956 there were 13 927 (estimated) deaths from tuberculosis in the United States Four to six new active cases are reported *each year for every death* The National Tuberculosis Association estimates that in 1956 there were 250 000 active cases in the United States

Epidemiology As man may be infected by human or bovine tubercle bacilli the source is usually traced to another person with tuberculosis or to a tuberculous cow Contaminated milk is seldom implicated in this country but elsewhere it is considered responsible for about 10 per cent of the cases of the disease among humans Much more often however human infection is the result of inhaling air contaminated by the person with "open" (*i e* cavitary) pulmonary tuberculosis as he coughs sneezes and expectorates heedless of hygienic care Other lesions such as superficial tuberculous sinuses may constitute sources and the possibility of transmission through contaminated urine or feces occasionally has to be considered Direct mouth to mouth transmission may occur particularly in nurslings As would be expected therefore many new cases of tuberculosis are discovered near the abodes of people previously afflicted In this sense the disease is frequently familial or household and it is also somewhat more prevalent among the personnel of hospitals or other institutions caring for tuberculous patients Infection has been shown to be almost inevitable among young children who in the home have close contact with the open case usually in an adult Infrequently infection occurs through the broken skin *e g* among laboratory workers handling fresh tuberculous specimens Rarely a fetus is infected by way of the blood stream from a tuberculous placenta or less often by aspiration of bacilliferous amniotic fluid into the lungs

Bacteriology Three varieties of tubercle bacilli have been known longest and best *Mycobacterium tuberculosis* var *hominis* *M tuberculosis* var *bovis* and *M avium* Man may be infected by the human or bovine varieties seldom by the avian Lower animals are infected most often by the bovine variant This varying pathogenicity may be used to help identify the variety involved Thus guinea pigs are susceptible to infection by bovine and human bacilli but not the avian rabbits are susceptible to the bovine and avian much less to human fowls usually are susceptible only to the avian The bacillus is a rod shaped organism distinguished particularly by its acid fastness to stains Granular forms have been described but these may be artefacts (Yegian and Porter) The bacillus grows slowly and aerobically on various culture media R J Anderson particularly has

* Compiled by Statistical Division New York Tuberculosis and Health Association

may follow soon after caseation The liquid collection is prone to break its bounds In the lungs it frequently sloughs and empties its contents into the bronchi a renal focus empties into the ureter A necrotic superficial lymph node commonly sloughs through the skin or if the node is deeply situated may discharge into the trachea or some other passage a vertebral abscess may dissect its way within the psoas sheath and rupture the skin of the groin Whatever the outlet sloughing and evacuation are accomplished not primarily by the mechanical disruption of healthy tissue but rather by necrosis and ulceration due to extension of the infection It is the caseous necrosis of the wall of a pulmonary vein for example which often establishes a channel by which bacilli gain access to the blood stream

After sloughing and excavation have occurred the damaged tissue is left with a defect which varies according to the structure of the particular part involved In the larynx the defect is apt to be a superficial ulcer in the middle ear a perforated drum and in the lung a parenchymal cavity Some of the defects especially if the discharge from them does not drain freely may be the seat of secondary infection with other bacteria

Healing and *repair* of tuberculous lesions may occur at various points If the infection subsides in the early inflammatory phase the exudation of cells and fluids ceases and resolution of the accumulated products follows usually at a much slower rate than with other bacterial infections If caseation has already set in as it does in most lesions of material size and duration resolution of the surrounding non necrotic exudate may occur but the necrotic centers still harboring bacilli remain to be dealt with Such caseous residues if propitious conditions last undergo slow fibrous organization with some drying and shrinkage Eventually the lesion may be converted into an irregular fibrocaseous mass or into a rounded structure enclosed wholly or in part by a fibrous envelope This fibrosis may extend well beyond the center of the lesion In time the caseous part of the fibrocaseous lesion may become infiltrated with mineral salts chiefly calcium phosphate from the body fluids The process may proceed through a "chalky" phase to complete calcification or ossification By this time the contained bacilli frequently

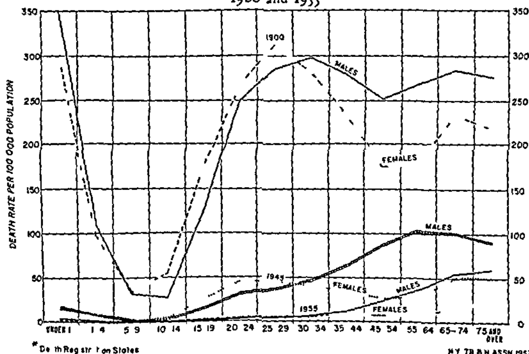


FIG 28 Additional curves (1945) are drawn in to indicate the accelerated decline of the death rates after specific chemotherapy became available The general application of this started about 1947

causes proportionately more deaths among American Indians and Chinese than it does among Negroes in the United States

Age and *sex* influence the behavior of the disease whether this originates in a recent primary infection or in a recent extension from remotely established lesions General ized tuberculosis is much more common in early childhood Chronic pulmonary tuber culosis characteristically begins to appear in the second and third decades The mor tality experience with relation to sex and age is shown in Figure 28 It will be noted that in the United States the prevalence of fatal tuberculosis is greatest among elderly men a phenomenon which is dupli cated in many other countries

Physiological and Psychological Influ ences Pregnancy aggravates tuberculosis in some women Impaired nutrition may lower resistance The increase in fatal tubercu losis in Europe during both World Wars seems to have been related largely to the drastic reduction of food which permitted a reactivation of previously latent pulmo nary lesions In World War II the disease was rife in German concentration camps such as Dachau and Buchenwald as well as certain prisoner of war camps where the nutritional deficiences of some inmates reached the edema level Anxiety and ten sion created by psychological maladjust ments seem to lower resistance There is some evidence that tuberculosis is more likely to develop in schizophrenics The death rate is usually high in institutions for the mentally ill but this seems now to be ascribable chiefly to intimate exposure and inadequate care and to be largely correctible by isolating the infectious cases

Environment Geographical location alone does not seem to be a major influence Tuberculosis is a serious problem both in the Alaskan Indians and in Puerto Ricans Social economic and occupational factors are much more important Ignorance poor housing and overcrowding all are recog nized as powerful evils *Occupation* which is a good index of social economic status illustrates this strikingly The death rate is highest among unskilled laborers and lowest among those in professions including physicians A specifically dangerous occupa tion with relation to tuberculosis is that which involves exposure to silicious dust *e g* metal moulding sandblasting mining stone cutting and polishing and manufac turing of abrasive soaps

Trauma Previously healthy traumatized tissue is not liable to be invaded by tubercu losis except by direct extension from an im mediately adjacent lesion Direct traumati zation of tuberculous tissue however may be aggravating Occasionally in pulmonary tuberculosis a severe trauma of the chest may result in such manifestations as hemoptysis bronchial dissemination of the infection or pleural rupture with secondary empyema

Intercurrent Disease Diabetes if uncon trolled especially in young people predis poses to serious tuberculosis The phenom enon was conspicuous before the discovery of insulin In hyperthyroid states native resistance may be relatively increased and Lurie finds experimental evidence that this may be due to greater activity of phago cytes and destruction of tubercle bacilli the opposite may be found in hypothyroid ism Pulmonary tuberculosis is a frequent complication of congenital pulmonic ste nosis but when present usually runs a relatively mild course in association with mitral stenosis Tuberculous patients fre quently withstand pneumococcal pneu monia well unless the functional reserve has been almost depleted previously Ne crosing pneumonia or abscess however may lead to the breaking down of an ar rested tuberculous focus and subsequent extension of the infection from it

Morbid Anatomy The earliest reaction of the body to infection with tubercle bacilli is an accumulation of cells at the site There is also some vascular congestion and exudation of fluid While some pathologists believe that this early accumulation con sists almost or entirely of a proliferation of local tissue cells which may go on directly to form the classic histological tu bercle Medlar submits experimental evi dence that this is not the case but rather that the neutrophilic leukocyte predomi nates According to him later develop ments depend on the rapidity of growth of tubercle bacilli Leukocytes may continue to accumulate forming an abscess which may heal or if not may proceed slowly to liquefaction—much more slowly as a rule than the abscess produced by most other bacteria When the reaction is not so intense the leukocytes may gradually be replaced by epithelioid cells (monocytes) and lymphocytes these may be precursors or accompaniments of healing

A frequent change in the early inflam matory lesion is *caseation* a form of co agulative necrosis which as the name im plies has the appearance and consistency of cheese This rather dry necrotic matter may remain as such for many months after which it may liquefy or liquefaction

severe infections of the blood which however may be continued over a period of time perhaps with free intermissions In this type of dissemination the natural clinical course instead of being rapidly fatal as in generalized miliary disease may be protracted while the lesions in their various sites such as the lungs lymph nodes serous membranes spleen kidneys and so on may enlarge caseate and show other local changes Small and single or infrequent infections of the blood may set up one or a few isolated lesions which may heal or progress to local disease *e g* in bone eye kidney skin and so forth Frequently there is a long period of latency before some of these local lesions exacerbate and become manifest clinically Ustvedt and his co workers found that this period ranged from five to more than fifteen years in the case of renal tuberculosis and was still longer with disease of the adrenal glands Hemic dissemination due to the invasion of an artery occurs but rarely Not infrequently hemic dissemination occurs as an early sequel of primary infection especially in young infants and as a terminal event in fatal chronic tuberculosis

Another common route of dissemination is *intracanalicular* a term suggested to indicate channels such as the respiratory alimentary and urinary canals (exclusive of lymph and blood vessels) The most familiar example is related to the presence of a tuberculous cavity in the lung The bacilliferous discharge from this source passes through the bronchi and is for the most part expectorated but sometimes is inhaled during breathing into healthy alveoli of one or both lungs setting up new secondary lesions this is known as *bronchial* dissemination The severity of the secondary lesions varies greatly depending somewhat on the rate of sloughing of the cavity the amount fluidity and bacillary content of the discharge and the general resistance of the patient Large and abrupt disseminations such as may occur during a hemorrhage from the cavity may lead to acute confluent tuberculous lobular or lobar pneumonia but the more common pattern is a succession of smaller secondary lesions at intervals varying from days or weeks to many months During periods of clinical arrest when there are no freely discharging cavities new secondary lesions seldom appear but the exacerbation and sloughing of old arrested lesions often marks a reactivation of these mechanisms and is the usual explanation of relapse In this way sooner or later chronic pulmonary tuberculosis often becomes established the lungs and pleura showing old fibrous scars along with new inflammatory and caseous lesions

Contact infection of the mucous membrane by the discharge from a pulmonary cavity may cause lesions in the bronchi trachea or larynx the last being a fairly common site Other loci include the middle ear infection here being carried more often via the eustachian tube than the blood stream the tongue and the lip (usually through abrasions) Infection seems to favor places where bacilli have fairly long contact Thus when pus from the lungs is swallowed as often in chronic cases the alimentary organs usually escape until the lower ileum cecum and ascending colon are reached and the passage of contents slows Tuberculous ulcers are found there in many advanced pulmonary cases By similar mechanisms the rectal crypts may be infected and an ischiorectal abscess may form

Other manifestations of *intracanalicular* dissemination are from the kidney to the ureter and bladder and from prostate to epididymis

From the foregoing it is easily seen that the lungs are peculiarly open to attack by tubercle bacilli which may find access through inhalational hemic and bronchial routes

Evolution of Primary Lesion The lung is the site of the primary lesion in more than 90 per cent of infected persons (Ghon) Other sites include the intestine (often ascribed to the ingestion of contaminated raw milk) tonsil skin and conjunctiva The pulmonary lesion is usually single and situated in a lower lobe or lower part of an upper lobe Progressive disease may ensue Meningitis and generalized miliary tuberculosis are relatively common sequels in early childhood while in adolescence and adult life the clinical manifestations are more often traceable to the excavation of the pulmonary lesion and the spread of infection by way of the bronchi Enlargement of the mediastinal lymph nodes is more often massive and extensive in children than in adults and there is a greater tendency for these extensively enlarged nodes to perforate the bronchi

GENERAL CONSIDERATIONS IN CLINICAL DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

Tuberculin Tests A typical reaction to a standard tuberculin test is a specific indica

die At any time if the bacilli survive the infection may be reactivated leading to an extension of the disease It is not uncommon to observe healing in one lesion while others progress Ulcers and cavities can be repaired only by fibrous organization and contraction The mucous membrane may grow back over a healed ulcer of the larynx for instance but destroyed alveoli of the lung are not restored Large cavities as of the lungs seldom heal completely by natural processes

An understanding of the time factor in healing is most important in clinical practice Marked resolution may be observed within several months but fibrous organization of the residual lesions is inevitably slow requiring many months or years In many cases largely because of the extent of caseous necrosis healing is incomplete and impermanent and the status at best can be regarded only as arrested

Chemotherapy may retard or halt active disease and accelerate healing but the essential processes of resolution and fibrous repair are not otherwise altered

Pathogenesis For many of the present concepts of pathogenesis we must look principally to the pathologist Interpretation of the findings is often difficult and the terminology used has sometimes been confusing In recent years there has been a tendency to discard such designations as *childhood type* and *adult type* of tuberculosis because they have no clear connotation Likewise *reactivation* or *exacerbation of disease* is suggested instead of *endogenous reinfection* to describe the renewed progression of lesions which previously had been inactive and perhaps partly healed

The inflammation which appears at the site of the primary infection is known as the *primary lesion* (in the lung sometimes called the Ghon focus) The combination of the primary lesion and that which usually appears simultaneously or soon thereafter in the tributary lymph nodes is the *primary complex* (Ranke) The complex may be incomplete in that the parenchymal or less often the lymph node focus may not be found but this is unusual A *reinfection lesion* is one caused by a new (exogenous) infection Pathological evidence of this is the finding for example of a recent lesion in the lung apparently unrelated to but existing with an old well healed and calcified primary complex The importance and frequency of reinfection (superinfection) in the presence of existing unhealed disease are not established So long as there is an unhealed focus in the body progressive disease is much more likely to originate from this than from an exogenous reinfection After the primary complex has healed fully the possibility of reinfection seems to be vastly greater Thus Medlar found at autopsy that progressive "minimal pulmonary lesions in the bodies of 23 persons under forty years of age were a part of primary disease in 91 per cent while in 73 over forty years of age similar lesions were due to reinfection in 72 6 per cent

Dissemination Before further consideration of the various phases of tuberculosis the routes by which the infection is spread in the body should be recognized Any such lesion may extend locally *i e* by continuity and contiguity depending somewhat on the nature of the tissue barriers Thus it often spreads broadly over the pleural surface but it seldom penetrates the parietal pleura and invades the chest wall unless the membrane is broken (*e g* by needle puncture) *Lymphatic** dissemination of the infection is observed most strikingly at the time of the primary infection as indicated by the tributary lymphadenitis it becomes lymphohemic if the bacilli are not retained in the nodes but are carried with the lymph—through the thoracic duct for instance—into the venous blood stream Uncommonly tuberculous lymphangitis may be set up along the route of spread Retrograde lymphatic extension *i e* against the lymph stream seldom if ever occurs

Two other common modes of dissemination depend on the tendency of lesions to slough and discharge after caseation One is *hemic* which is explained almost always by a caseous lesion invading and destroying the wall of a vein thus allowing bacilli to enter the blood stream The usual site is a pulmonary vein but others are also recognized such as a vein in a caseous prostate gland The results of hemic dissemination vary according to a number of factors the most important apparently being the mass and rate of discharge of bacilli from the caseous focus Acute generalized miliary tuberculosis is usually interpreted as the result of an abrupt infection of the blood with an overwhelming mass of bacilli Subacute and protracted generalized forms seem to be related to less

* Certain terms dignified by usage are in their literal meaning quite incorrect as applied in pathogenesis For clearness in these paragraphs therefore the terms *lymphatic* *lymphohemic* *hemic* and *bronchial* are used instead of *lymphogenous* *lymphohematogenous* *hematogenous* and *bronchogenic* respectively

ease is still in its incubation period (five or six weeks after the primary infection sometimes longer) (2) if existing tuberculous lesions are thoroughly healed and calcified (3) in some terminal cases of tuberculosis (4) in the presence of severe acute exanthemata (5) in poorly understood anergic states such as that which occurs in cases of sarcoidosis and (6) if the dose of tuberculin is too small Following the administration of cortisone or corticotropin the tuberculin sensitivity of the skin may be temporarily diminished

Demonstrating the Tubercle Bacilli * When possible the demonstration of the presence of tubercle bacilli is the final proof of the tuberculous nature of a lesion Furthermore in clinical practice the recovery of the bacilli may be taken in most instances as evidence that the lesion in question is active or only partly healed The reason for this is the fact that the organism does not escape readily from the lesion until caseation liquefaction and ulceration have occurred Unlike most other bacterial pneumonias for instance the early tuberculous pneumonia is composed of an exudate which is relatively dry and possibly coagulated and on this account does not "leak" into the bronchus moreover at this time there is little or no tuberculous bronchitis Bronchial discharges do not start until the parenchymal lesion sloughs not until then are tubercle bacilli likely to be demonstrated in the sputum According to the same principle the resulting defect or cavity cannot be said to have healed *as long as bacilli are demonstrable* The same concept applies in other situations such as the finding of bacilli in the urine with respect to early tuberculosis of the kidney Even after a lesion starts discharging its purulent contents it may do so slowly and in small quantities bacilli may be recovered therefore only from isolated purulent particles or in a collection of the discharge such as sputum taken during several days A few organisms from an early sloughing renal lesion may be greatly diluted in the urine and therefore hard to recover consequently they must be concentrated again by centrifugation or some other method Similarly in serous effusions and in the pus of abscesses there may also be great dilution requiring artificial concentration before the bacilli can be demonstrated In view of such circumstances therefore failure to detect the bacillus is not accepted as proof of its absence However there are particular relationships in which this failure is highly significant such as a "negative" purulent sputum which is being expectorated in considerable quantities from a pulmonary cavity In such circumstances the lesion is unlikely to be tuberculous

Cultural methods and *animal inoculation* are of great assistance if the specimens are carefully prepared The former are more convenient and if skillful and meticulous techniques are used they are as efficient as animal inoculation In either case the results may not be known for six or eight weeks Consequently special methods have been developed to speed up bacterial growth They include several media developed by Dubos and Middlebrook a chick embryo medium suggested by Bunn and a slide culture method proposed by Pryce The characteristics of *virulence* of tubercle bacilli have been studied by Middlebrook Dubos and Pierce who observed the virulent forms growing on culture media in long serpentine cords Dubos and Middlebrook have also described a cytochemical reaction with neutral red which appears characteristic of these forms H Bloch has identified a material of lipid character ("cord factor") which appears to coat the surface of the bacillus and to be closely *related to its virulence Organisms obtained* from patients before they are treated with specific drugs are almost always found to be uniformly pathogenic for guinea pigs Variations in potential virulence are not known to be related to manifestations of human disease except in rare instances such as lupus vulgaris (Griffith) Attenuation of virulence is often observed however in bacilli obtained from patients who have been treated with isoniazid these strains are usually found to be isoniazid resistant and catalase negative Although their ability to produce tuberculosis in guinea pigs may be greatly reduced they may still retain their virulence in mice and hamsters No other drug has been shown to have such effects

One of the identifying marks of the tubercle bacillus is its *acid fast staining* by certain dyes This characteristic is brought out by fixing the prepared specimen on a microscopic slide and applying the stain according to one of a number

* Various bacteriological techniques adapted especially for the problems of tuberculosis are described in a booklet Diagnostic Standard which may be obtained from the National Tuberculosis Association 1790 Broadway New York City A more comprehensive treatise is the book of Willis and Cummings Diagnostic and Experimental Methods in Tuberculosis Springfield Illinois Charles C Thomas 1952

tion of the presence of a tuberculous lesion somewhere in the body beyond this fact there is always the implication that the lesion probably contains living tubercle bacilli

Indications for Testing The tuberculin test is a valuable means of determining the prevalence of infection in a community It often is a tracer of sources of infection *e g* a young child who reacts to tuberculin probably has been in contact at home or elsewhere with some person with tuberculosis in the infectious state In such ways tuberculin testing is useful in communities where the disease is of low prevalence and is likely to exist in nests In clinical practice it is often distinctly helpful in diagnosis

Materials and Techniques Of the many tuberculins prepared from cultures of tubercle bacilli the two best known and most often employed are Purified Protein Derivative (PPD) developed by Seibert and Old Tuberculin (OT) first prepared by Robert Koch The former is widely favored and is recommended by the National Tuberculosis Association A special batch known as PPD S has been adopted by the World Health Organization as the international *standard tuberculin* The *international tuberculin unit* (TU) is specified to be that amount of PPD which is equal in potency to 0 00002 mg of PPD S

For general use with the *intracutaneous* (Mantoux) test a solution is prepared so that 0 1 ml contains 5 TU of PPD or an equivalent amount of OT (This is approximately 0 05 mg of OT of standard potency and is administered as 0 1 ml of a 1 2000 dilution of OT) This precise dose is recommended especially by C E Palmer and his associates because larger doses are thought sometimes to elicit reactions which are not specific for tuberculosis

The test is usually performed on the volar surface of the forearm Using a calibrated syringe and a 25 or 26 gauge needle 0 1 ml of the solution containing the specified dose (5 TU) is injected into the skin close to the surface producing a wheal The site is inspected and palpated within forty eight to seventy two hours after the injection Empirically an area of induration greater than 5 mm in diameter is considered to represent a positive reaction lesser induration is doubtful and may be nonspecific The central area of induration is usually surrounded by a zone of erythema but erythema without induration is not interpreted as a specific reaction

Tuberculins which are presently available are known to vary considerably in their potency and may not conform to the standard Partly on this account and partly because of time honored practice many physicians confronted with clinical diagnostic problems test initially with 0 1 mg of OT (0 1 ml of a 1 1000 dilution of OT) or sometimes with a lower dose (0 01 mg of OT) if no reaction occurs a second test is often done with ten times the initial dose of OT Similarly in the presence of disease of doubtful etiology some test initially with 0 00002 mg of commercially available PPD going on to a higher dose for a second test if the first is negative Severe reactions may result in the formation of a vesicle with necrosis of the tissues and there may be pink streaks of lymphangitis extending up the forearm and palpable slightly tender nodes in the axilla A *percutaneous* or *patch test* is performed by applying to the skin a strip of adhesive tape on which a piece of gauze saturated with dried tuberculin is attached The local reaction is represented after forty eight to ninety six hours by a red papular and occasionally slightly vesicular eruption The patch test is said to approximate in accuracy the Mantoux test using 0 1 mg of OT most observers however do not rely on it as a fine index of tuberculin allergy Its chief virtue is the simplicity of its application it may be placed on the back which is desirable for children If no reaction occurs the more dependable Mantoux test may be used A multiple puncture test (Heaf) is performed with a special instrument and is reputed to be quick and painless The older scarification (Pirquet) test is not often used today

In addition to the local reaction to any tuberculin test there may be a constitutional reaction with fever and malaise and less often a focal reaction of inflammation about tuberculous lesions These should be guarded against by carefully selecting the dose of tuberculin

Interpretation of Cutaneous Hypersensitivity to Tuberculin An infant who reacts to tuberculin is assumed to have an active tuberculous lesion due to a recent primary infection In older persons the lesion may be old and fibrotic and therefore inactive In the presence of manifest disease of uncertain causation a reaction is of little or no practical diagnostic value but no reaction is significant since the disease in these circumstances is unlikely to be tuberculous The test is not a measure of immunity or of the degree of activity of the disease in the individual case The reaction may be depressed or absent (1) if the dis

are interpreted to correlate closely with clinical manifestations However in all of these tests the exceptions are too numerous to justify the routine use of the tests either for differential diagnosis or for the determination of the activity of a tuberculous process A number of observers among whom may be mentioned Florence Seibert Zitrin and Maher and their respective associates have been interested in the determination by electrophoretic or chemical methods of the *protein fractions* of the *serum* and some suggest rather guardedly that variations noted especially in serial tests may be of prognostic value During active phases of the disease there is a rise in the gamma globulin fraction and the albumin decreases the latter returns to normal as the activity of the disease subsides while the gamma fraction according to Maher remains slightly elevated With these initial disturbances there may also be an elevation of the alpha fractions and less significantly of the beta Hirsch and Cattaneo found an increase in *protein bound carbohydrate* which they consider to bear a close relationship to the clinical activity of tuberculous processes They think chemical determinations may suffice for clinical purposes and Zitrin has the same view with respect to globulin C *reactive protein* also appears in the serum of patients with active tuberculosis Walsh and his associates found its presence to be correlated in active disease with the erythrocyte sedimentation rate but the absence of C reactive protein was a better index of inactivity of the disease than the latter In the late stages of tuberculosis there may be other changes including a lowering of the blood volume and of the content of mineral salts enzymes and vitamins *Bacteremia* must occur obviously during hemic disseminations and occasionally may be demonstrated culturally Most efforts however are unsuccessful probably because of the degree of dilution of the bacilli and their rapid disappearance into phagocytes which become immobilized

There is no reliable specific test of resistance or immunity against tuberculosis nor is there a good prognostic test in chronic forms of the disease These factors are best judged by a summation and evaluation of routine clinical roentgenographic and laboratory data

Toxicity of Tuberculosis No true toxin has been identified as a product of the tubercle bacillus Various chemical components of it and by products of its growth in artificial culture media can be introduced into the tissues of a healthy animal without appreciable harm If the tissues are allergic because of previous infection however there may be definite and severe reactions as with the tuberculin test The mechanisms of this phenomenon are complex and unclear The toxicity is characterized by its relative mildness In the early phases of tuberculosis often enough there are no subjective general symptoms Usually it is only after the disease has advanced and caused considerable involvement of tissues that loss of weight malaise and fever occur This disproportion between volume of disease and mildness of symptoms is almost unique and often gives a clue to the diagnosis

In some cases the chronic toxicity of the disease predisposes to the development of amyloidosis However the majority of fatal pulmonary cases are not associated with this complication It is observed most often in association with secondarily infected lesions of the bones and joints in mixed infection tuberculous empyema and in cases of severe intestinal tuberculosis complicating pulmonary disease

The symptomatology local as well as general is considered in more detail in the sections dealing with various forms of the disease Emphasis is placed on the pulmonary form because this is the most frequent in clinical practice

Likewise the principles of treatment will be described with special reference to tuberculosis of the lungs and to problems related to other specific sites of the disease Since the antituberculosis drugs have certain similar effects on all forms of tuberculosis a general description of their actions will be given at this point

SPECIFIC CHEMOTHERAPY FOR TUBERCULOSIS

The *in vitro* growth of the tubercle bacillus is inhibited by an enormous range of organic compounds few of which exhibit *in vivo* activity To merit classification as a tuberculostat of interest therefore a compound should possess marked activity *in vivo* (H H Fox) To be of practical value it may be said in addition the compound should not have serious toxic effects when administered in effective therapeutic doses

The searches of investigators during the centuries culminated in the discovery of effective compounds as well as recognition of the therapeutic properties in others which were known but not previously tested In 1944 *streptomycin* derived from *Streptomyces griseus* was announced as a discovery by Schatz Bugie and Waksman Feldman and Hinshaw soon observed its tuberculostatic influence in experimental animals and treated patients In 1946 Lehmann reported the favorable effects of para aminosalicylic acid (PAS) The announcements of other discoveries followed these included amithio-

of techniques usually the Ziehl Neelsen With this a carbol fuchsin stain is applied followed by acid alcohol to bleach all organisms except the mycobacteria which retain the red color With rare exceptions such acid fast organisms in expectorated sputum are tubercle bacilli However gastric specimens taken when the sputum is negative should be cultured since these often contain nonpathogenic saprophytic mycobacteria ingested with food such as raw vegetables and fruits Similarly acid fast saprophytes indigenous to the cerumen of the external auditory canal and the external genitalia (smegma bacillus) must be differentiated when specimens of pus or urine are taken for diagnosis These nonpathogenic and atypical mycobacteria may be distinguished by their cultural characteristics and in other ways (See Other Mycobacterial Diseases p 293)

Secondary infection of tuberculous lesions including effusions and abscesses rarely occurs by way of the blood or lymph streams Its presence usually is explained by communication with the respiratory or alimentary canals or with the external surface of the body after a sinus fistula or cavity has formed then the common pyogenic bacteria may gain access Occasionally they are introduced by faulty technique as in thoracentesis The effect may be serious if drainage is poor or if there is a dead space causing a mechanical hindrance to healing (*e g* pleural empyema) or it may be inconsequential Thus a tuberculous pulmonary cavity is not usually aggravated by secondary infection unless a blockage of the bronchi interferes with free drainage of the discharges

Surgical Biopsy and Diagnostic Aspiration In difficult cases especially when it is urgent to make the diagnosis promptly so that appropriate treatment may be started biopsies of tissues which are obviously or probably involved in the disease may be obtained through a surgical incision or by the use of a special needle When granulomatous lesions are found in the specimen special bacterial staining is often necessary to help make the distinction between tuberculosis fungus infection sarcoidosis and beryllium granulomatosis the demonstration of true caseation however is usually accepted as presumptive evidence of tuberculosis The aspiration with syringe and needle of serous tuberculous effusions is usually harmless if good judgment and technique are used If the effusion is purulent and teeming with tubercle bacilli special precautions should be used to avoid infection of the needle track which sometimes leads to necrosis and the formation of sinuses and fistulas Precaution should also be exercised to avoid the perforation or laceration of underlying structures for this reason it may be preferable to obtain the specimen of fluid by making a small surgical incision This *for instance should avoid* puncturing the intestine if it should be bound to the parietal peritoneum by tuberculous or other plastic exudate The danger *of reactivating or aggravating a local lesion* by any of these procedures or of spreading the infection may be minimized by chemotherapy

Changes in the Blood of Tuberculous Patients In the early phases of tuberculosis significant changes in the cells of the blood are seldom detected During insidious progression of the disease there may be no rise in the total number of *leukocytes* though there may be some increase of the young forms and of monocytes while lymphocytes may be relatively decreased During acute exacerbations these tendencies may be greatly accentuated the polymorphonuclear leukocytes may rise to 12 000 to 18 000 per cu mm (seldom above 20 000) while the percentage of neutrophils also increases but not often above 80 per cent Higher ranges always raise the question of some other bacterial infection and in this way are often helpful in differential diagnosis If and when the disease settles back to a quiescent chronic or healed state the numbers and proportions of leukocytes usually return almost or entirely to normal The *erythrocytes* and their *hemoblobin* content usually remain normal until there has been considerable progression of the disease when slight anemia may appear Severe grades are observed in the late stages of the disease especially if it is complicated with intestinal involvement or amyloidosis

The *sedimentation rate* of the erythrocytes is accelerated in almost all the febrile phases of tuberculosis Also it may be accelerated in many of the afebrile phases and thus may be a more sensitive index of activity than the temperature curve Its value is limited by the fact that it is *not* specific for tuberculosis and may be normal in the early active phases and also later when the lesions have become chronic although not healed The same *limitation* applies to other activity tests of which there have been many Specific *complement fixation* and *hemagglutinin tests* for *tuberculosis frequently yield findings* which

months or longer may contain numerous tubercle bacilli which take the acid fast stain but fail to grow in artificial media or to produce disease in the usually susceptible animals There is evidence to indicate that some of these organisms are dead and that the habits of growth and reproduction of others are profoundly modified The same phenomena have been identified in lesions from patients who have never had specific chemotherapy but the time required for such modifications under natural conditions appears to be much longer In contrast tubercle bacilli obtained from "open cavities of the lung (i e with free bronchial communications) are found more often to be demonstrably viable and virulent an exception with respect to isoniazid will be mentioned

As mentioned before the effects of specific chemotherapy on tuberculous lesions and clinical symptoms do not differ essentially from the effects of natural regression of the disease without such aid However with the relatively rapid bacteriostasis induced by chemotherapy the favorable response is usually more surely predictable more prompt and more consistently sustained So far as known chemotherapy merely holds the infection effectively in abeyance and thus allows nature to take its course unhindered by the continuing attack of actively growing tubercle bacilli When the natural defenses are poor or entirely lacking even the most potent drugs are unavailing The well known but immeasurable variability of these defenses helps to account for differences in the behavior of individual cases and to support the concept that each patient is a law unto himself

In most cases the early response to treatment is a cessation of exudation in and about lesions and a diminution of constitutional symptoms As fever subsides for instance edematous swellings recede and the pain from this tissue tension eases and vanishes Accumulated exudate then is removed by resolution absorption and drainage here again the rate is variable Fibrous repair ensues and proceeds its adequacy in the long run depending on the damage done beforehand by the necrosing effects of the infection Eventually as with any antituberculosis treatment the outcome is determined not only by this healing but also by the persistence of partly repaired necrotic ulcerous excavated tissue which harbors tubercle bacilli ready to renew the attack

Action of Individual Drugs *Streptomycin* in a dilution of 1 56 micrograms per milliliter of artificial culture medium completely inhibits the growth of almost all human and bovine strains of tubercle bacilli the avian strain is said to be more resistant The action of the drug is somewhat inhibited in an acidic medium or in one containing nucleic acids conditions which exist in some tuberculous abscesses and cavities Resistant strains assumed to exist in rare numbers in any wild" bacterial colony proliferate *in vitro* and *in vivo* so that after about four weeks of exposure to the drug they begin to predominate At the end of 120 days 80 to 90 per cent of the cultures are found to be resistant to more than 10 micrograms of streptomycin per milliliter many will resist the effects of 1000 micrograms or more However the virulence of resistant organisms is not appreciably altered In clinical practice the emergence of resistance is found to depend more on the duration of treatment than on daily dosage however the rate of assuming predominance is slower if the drug is given only twice a week in 1 0 gm doses Streptomycin is generally administered by intramuscular injection if indicated it may also be given intrathecally Oral administration is ineffective for tuberculosis because of the poor absorbability of the drug and inhalation of the aerosol is avoided because of the lack of demonstrated advantage and its tendency to cause a sensitization of the tissues

Toxic effects principally on the vestibular apparatus are frequent when streptomycin is administered intramuscularly in doses amounting to 2 0 gm daily for two to four months or longer their incidence is much less when the dose is reduced to 1 0 gm daily and still less on a regimen of 1 0 gm twice weekly Vestibular dysfunction appears as vertigo nausea vomiting ataxia and partial or complete loss of response to caloric stimulation if severe this loss may be permanent but there may be partial recovery from mild damage Less frequently impairment of the auditory function may occur usually preceded by tinnitus Deafness is of the perceptive type according to Winston Other disturbances include dermatitis which occasionally may be severe and exfoliative eosinophilia and renal damage Neurotoxic effects on the fetus have not been reported and it is considered safe to give the drug during pregnancy A few nurses and others who have direct contact with streptomycin in handling it are observed to develop hyper

zone (4 acetylaminobenzaldehyde thiosemicarbazone) and a number of other related compounds and viomycin (derived from *Streptomyces puniceus* and *Streptomyces floridae*) Meanwhile drugs which are distinguished for their action against other bacteria were also found to have some tuberculostatic effect these include especially diaminodiphenyl sulfone and its derivatives (Promin Diasone Sulphetrone and Promizole) and oxytetracycline (Terramycin) In 1952 Robitzek and Selikoff reported strikingly favorable effects of isoniazid (isonicotinic acid hydrazide) and iproniazid (1 isonicotinyl 2 isopropyl hydrazine) in tuberculous humans Their work was preceded by the experimental investigations of Grunberg and Schnitzer Zieper and Lewis Bernstein Steenken and Wolinsky Benson Rubin and the associates of all these Also in early 1952 the antituberculous activity of pyrazinamide a derivative of nicotinic acid was demonstrated in humans by Yeager and his associates after laboratory studies by Kushner and Malone and their respective associates The antituberculous activity of cycloserine an antibiotic discovered by Harned and Kropp and isolated from *Streptomyces orchidaceus* was reported by Epstein and others in 1954 The discovery of another streptovaricin obtained from *Streptomyces spectabilis* was announced in 1956 by Siminoff Smith Sokoloski and Savage Both of these have considerable activity also against a number of other bacteria (Another antibiotic kanamycin has been isolated by Umezawa and his associates from *Streptomyces kanamyceticus* Preliminary reports indicate that this has some properties similar to those of neomycin but it is less toxic It appears to have significant activity against tuberculosis in animals and is receiving clinical trials)

As each of these agents became available they received clinical testing in various parts of the world The reports clearly indicated some merit in each compound It was soon appreciated however because of the known wide variations in the natural course of tuberculosis and the complexity of the problems implicit in the new treatments that organized studies of many hundreds of patients would have to be undertaken Such organization in many cooperating hospitals was arranged by the United States Public Health Service the United States Veterans Administration Army and Navy Hospitals and the British Medical Research Council and this together with thousands of individual efforts has accomplished great progress

The relatively high potencies of streptomycin and isoniazid have been satisfactorily demonstrated PAS while less effective has retained an important place for reasons to be mentioned The other drugs enumerated above have relatively limited effects and several have all but fallen into disuse especially since the advent of isoniazid At the start each drug in its turn was tried singly this had the virtue of demonstrating any toxic properties and the degree and range of therapeutic effects It soon became evident that almost all the compounds and certainly the more potent of them when given to patients suppress the growth of offending tubercle bacilli except those which are drug resistant these resistant strains then may take over the field and escape the effects of any further therapy with the given drug Such drug resistance becomes manifest at varying rates but commonly within two to four months after the start of treatment As a consequence the early favorable response frequently is followed by a relapse Then it was found that the growth of resistant strains may be suppressed to a greater or lesser extent by exposing them to drugs of another class and this was the genesis of combined therapy *i e* administering two or more drugs simultaneously Regimens employing two drugs are effective in preventing the proliferation of resistant strains for long periods of time *at least four months and in most cases apparently for a year or more* Although under certain conditions such as extremely acute disease the use of three-drug regimens may have some additional influence in delaying manifestations of drug resistance this superiority appears to be slight and not demonstrable in most clinical situations Usually it is considered wiser to hold one very potent drug in reserve for use in meeting possible needs such as a later relapse Drugs are not usually prescribed singly for the treatment of active disease but isoniazid is sometimes given alone (*e g* during the administration of adrenal corticosteroids) as a prophylactic against the reactivation of latent tuberculous lesions

Common Effects of Chemotherapy The mechanisms of antimycobacterial action of the drugs appear to be complex according to various studies Whatever these may be the outward manifestation is the failure of susceptible organisms to reproduce at least at the usual rate so long as they are exposed to effective quantities of the given drug This interference with the reproductive cycle may continue in the tissues for many months then after discontinuance of treatment bacterial activity may sooner or later resume its familiar course Lesions removed surgically may yield organisms which grow in animals or in artificial media In such instances the effect is obviously more or less prolonged *bacteriostasis There is other evidence* from the laboratory that in certain circumstances some of the bacteria actually may be killed by specific drugs and this is thought by Middlebrook and others to apply especially to young forms It has been found by many that more or less encapsulated lesions of solid caseous composition removed surgically from the lungs of patients who have been treated with drugs for four

a daily oral dosage of 5 mg of isoniazid per kg of body weight divided into three doses of about 50 to 100 mg each will maintain an adequate therapeutic concentration in the blood and other tissues in urgent cases such as those of meningitis the dose is usually doubled partly because the cerebrospinal fluid concentration is found to be only two thirds that of the serum In practice the response of tuberculosis to such doses of isoniazid (given with some other antituberculosis drug) is usually satisfactory However there are exceptions and some of these have been ascribed to the rapid metabolism and elimination of isoniazid Hughes Schmidt and Biehl (1955) reported marked variations in this process especially in treated tuberculous patients The output of free isoniazid and its hydrazones (both biologically active against the tubercle bacillus) in the urine was found to be in inverse proportion to that of acetyl isoniazid and isonicotinic acid (biologically inactive) The pattern of metabolism was shown to be constant in individuals but to vary widely from one patient to another Interest has centered on the process of acetylation which results in inactivation of the drug Kass and his associates (1957) report that approximately one third of their patients were found to be rapid inactivators and suggest compensating for this by administering 8 to 16 mg of isoniazid per kg daily together with 10 gm of PAS or PABA This they claim will be adequate for 95 per cent of white Americans The use in this way of PAS or PABA is based on the observation by Morse *et al* (1956) Bell and Mitchell (1957) and others that these and other aromatic amines compete in the process of acetylation and thus spare isoniazid in its free and active form A method for the quantitative determination of isoniazid and PAS in fluids of the body introduced by Maher and his associates (1957) may serve in this respect as a guide of proper dosages

Since the hydrazones of isoniazid are also active against the tubercle bacilli several of these and other compounds have been investigated for possible clinical usefulness especially since some are thought to have a low order of toxicity These include INH G (Galatone Mycobactyl 1) a glucuronolactone derivative INSH (Salizid) a hydrazone with salicylaldehyde Verazide (3 4 dimethoxybenzal isonicotinyl hydrazone) and Phtivazid With some of these the therapeutic effect is thought to depend somewhat on the liberation of free isoniazid in the body In cyanacetic acid hydrazide an aliphatic ring is substituted for a pyridine ring of isoniazid and this modification is also tuberculostatic However it has not been found to possess advantages in clinical use and it does not have any effect against isoniazid resistant tubercle bacilli

Para aminosalicylic acid in concentrations of approximately 1 5 to 2 0 micrograms per milliliter inhibits the growth of tubercle bacilli in artificial culture media This inhibitory power may be greater or less in media of varying composition and it is assumed that the effects *in vivo* also vary according to the nature of the diseased tissue The efficiency of PAS in clinical treatment is significant but less than that of isoniazid or streptomycin Among patients treated with PAS alone for four months and continuing at that time to discharge tubercle bacilli the organisms have been found to be resistant to 10 micrograms or more of the drug per milliliter of artificial culture medium in 50 per cent or more of the cases PAS is rapidly metabolized in the body largely by acetylation and excreted but following the usual dosage a concentration of 2 0 to 5 0 mg per 100 ml is maintained in the blood In practice 12 to 15 gm of the drug are prescribed to be taken daily by mouth this is divided into three equal doses and taken after meals A common problem is that caused by gastrointestinal irritation manifested by diarrhea nausea and vomiting in varying degrees To overcome or mitigate this numerous devices have been tried including the use of solutions (which deteriorate rapidly and liberate toxic substances) capsules tablets and coated granules A resin complex with PAS (Rezipas) is more tolerable by some patients also the sodium potassium or calcium salts These and a number of other PAS compounds are reputed to have advantages but the sodium salt is preferred generally if it is well tolerated None of them can be held blameless in the production of hypersensitivity with febrile and other reactions which are not uncommon and may be dangerous In some patients desensitization starting with minute doses of the drug and gradually increasing has been successful but others may never become tolerant In some instances PAS causes hypoprothrombinemia of slight degree (Linner 1953) also it has been found to interfere in some with the conversion by the thyriod gland of iodine to the organic iodide (Sutherland 1953) During pregnancy or in the presence of congestive heart

sensitivity to the drug simple preventive measures such as wearing rubber gloves seem to be effective

Dihydrostreptomycin has bacteriostatic effects similar to those of streptomycin and has been used in the same dosage While dihydrostreptomycin causes less frequent disturbance of vestibular function deafness is a more common result of its use the onset may be rather abrupt and it may not appear until a few weeks after the treatment has been discontinued Other toxic effects are much like those of streptomycin though dihydrostreptomycin may be well tolerated by patients who are hypersensitive to streptomycin

Several devices have been tried to avoid the neurotoxic effects of these drugs These include substituting a combination of half the usual dose of the two forms (*e g* 0 5 gm of streptomycin plus 0 5 gm of dihydrostreptomycin) for the full dose of either alone or administering streptomycin in the form of the pantothenate Except in the acute forms of tuberculosis however the usual practice is to restrict the dose of streptomycin to 1 0 gm and to administer this only at intervals of two or three days Dihydrostreptomycin may be substituted for streptomycin when indicated but the former has no effect against bacilli which are resistant to the latter and vice versa

Isoniazid is a superior therapeutic agent against tuberculosis As *iproniazid* produced troublesome toxic effects when given in therapeutic doses it is not in general use at present Isoniazid inhibits the growth of virulent tubercle bacilli in culture media in concentrations of 0 05 to 0 25 microgram per milliliter Elmendorf and his associates found plasma concentrations of the drug five to ten times these concentrations at the end of three hours in patients given doses totalling 3 mg per kilogram per day The drug may be given orally and also parenterally Isoniazid passes through tissue barriers readily and when taken by mouth it is found in considerable concentration in the cerebrospinal fluid The drug penetrates caseous tuberculous lesions (R W Mathei *et al*) apparently more readily than streptomycin It also inhibits the growth of tubercle bacilli within isolated rabbit macrophages in a concentration of 0 05 microgram per milliliter compared with 25 micrograms of streptomycin required for a similar effect (Mackaness and Smith)

When isoniazid is administered alone for periods of six to seven months and tubercle bacilli are still present in the sputum these are found to be resistant to 5 micrograms of the drug per milliliter of medium in 50 per cent or more of the cases (U S Public Health Service Study) As mentioned above (Cultural Methods and Animal Inoculation p 253) a unique feature of some of these strains is their loss of pathogenicity for some species of animals but not for others The significance of these phenomena is not clear To what extent if any such attenuation of virulence applies in tuberculous persons is not known Some have been observed to continue with progressive disease while discharging bacilli of low pathogenicity for guinea pigs but as a rule such patients do well There are also isolated instances of persons developing disease anew after infection with bacilli of such character

A great advantage of isoniazid is its relatively low toxicity The development of hypersensitivity to this drug is very infrequent and when it does occur it is sometimes in patients who have become hypersensitive to PAS and/or streptomycin previously or simultaneously The condition manifested by fever eosinophilia neutropenia hemolytic anemia purpura and lymphadenopathy has infrequently been serious and even fatal Usually however it subsides when the administration of the drug is discontinued and appropriate treatment is given Isoniazid taken by mouth does not irritate the gastrointestinal mucosa (In large doses [25 mg per kg] it may cause hepatic damage in animals) In adult humans doses of 20 to 30 mg per kg daily prove to be toxic in almost half of the patients and this has been found to be largely a consequence of the development of pyridoxine deficiency in children such deficiency is not observed (Lincoln and Morales 1957) Toxicity is manifested most often by peripheral neuritis muscular twitching hyperreflexia difficulty in micturition and constipation rarely optic neuritis clonic convulsions or temporary psychoses The occurrence of toxic symptoms is infrequent during the administration of 5 to 10 mg of isoniazid per kg daily then they are mild and usually disappear as the dose is reduced With very large doses peripheral neuritis is usually prevented by the simultaneous administration of pyridoxine orally Carlson and his associates suggest for adults 25 mg of pyridoxine for 8 mg of isoniazid per kg per day and 50 mg of pyridoxine for 16 mg of isoniazid per kg per day

Until recently it had been assumed that

be given in four equally divided doses separately This seems to avoid peak blood concentrations which are liable to be toxic Some interest is now (1957 1958) centering on the clinical study of the therapeutic merits of a daily regimen of 4 0 to 5 0 mg of isoniazid per kg of body weight plus 0 5 gm of cycloserine divided into two equal individual doses While the early reports indicate that objectionable side effects are less than those of a regimen of isoniazid *and PAS the therapeutic efficacy of the* latter is superior It is generally agreed that cycloserine should be administered only in a hospital where close observation of the patient s course can be maintained

Oxytetracycline tetracycline and *chlortetracycline* are relatively weakly tuberculostatic *in vivo* and approximately equally so according to Hobby although she found the first of these to be more active than the others *in vitro* Oxytetracycline has had the more extensive clinical trials Administered in company with a more potent drug the eventual predominance of strains of tubercle bacilli resistant to the latter is delayed but this may not be for a long time A combination of viomycin 2 0 gm intramuscularly twice weekly and oxytetracycline (Terramycin) 2 0 to 4 0 gm orally daily is suggested by McMurdock and Stewart as a second defense regimen *i e* after the effects of a better combination have been exhausted

Streptovaricin and *kanamycin* are newcomers undergoing trial The former appears to be less effective in clinical treatment than streptomycin or isoniazid Claims have been made that the later is a potent antituberculous drug without serious toxicity Preliminary accounts of clinical experience with the drug mention the occurrence of cylindruria and neurotoxicity but the gravity of these is not yet known

Amithiozine and the *sulfones* have relatively weak bacteriostatic effects in doses which can be tolerated by most patients Amithiozone may cause disturbances of hepatic function and blood formation although these usually correct themselves when the use of the drug is discontinued *Hinconstarch* described by Barry (1954 1956) as a polymer from periodate oxidized potato starch with an equimolar mixture of isoniazid and p aminobenzalthiosemicarbazone (pABT) has been found effective in the treatment of tuberculosis However Katz and his co workers (1957) observed toxic effects suspected to be chargeable against the thiosemicarbazone fraction which with the isoniazid may be liberated in the body

Neomycin is tuberculostatic but has highly toxic effects on the kidney and auditory function On this account it is not considered safe to be included in any of the usual regimens However it is sometimes applied topically in infected tissues because of its activity against bacteria other than tubercle bacilli *e g* in the infected pleural cavity after a surgical operation in this area

Among many other substances which have been studied because of their tuberculostatic activity may be mentioned substituted thioureas diphenyl compounds thioethyl compounds and sulphydril compounds

Combined Regimens In the present-day treatment of tuberculosis with drugs two important principles are to be recognized The first is that such therapy restrains the multiplication of drug susceptible tubercle bacilli and leads to the death of some but has no effect whatsoever on bacilli which are resistant to the drugs being employed It cannot be assumed that lesions are sterilized particularly the caseous necrotic lesions which are present in all cases of clinical disease The second principle is in a sense a corollary of the first namely since it should be assumed that tubercle bacilli continue living in the body throughout any course of treatment and for an indefinite time afterwards and since a lengthy period of time is required for lesions to become so firmly healed that the remaining bacilli will be permanently contained the treatment should be planned to exert its bacteriostatic effect continuously for a long time—many months or even years This is achieved at least in part by administering two drugs concomitantly (sometimes three in urgent cases) in a regimen which is known usually to be effective and relatively safe and continuing this without interruption according to the degree of response for an arbitrary period of time beyond the point at which clinical symptoms of active infection have disappeared and anatomical repair of the lesions seems to be well on its way The time required to arrive at this point varies greatly according to circumstances particularly the extent of destructive disease and usually will be shortened by rest treatment in the early and active stages

Comprehensive and statistically controlled studies in United States Veterans Administration and other hospitals have provided many sound guides for the choice

failure the potassium salt may be substituted for the sodium

Viomycin is reported by Steenken and Wolinsky to have about 25 per cent of the potency of streptomycin in tuberculous animals This drug is active against strains of tubercle bacilli which are resistant to other drugs and may be used in situations where the effects of other chemotherapy have been exhausted In daily doses of 50 mg per kg it may have toxic effects including renal damage hypokalemia and deafness Regimens which have been found to be helpful and usually well tolerated when needed are (*a*) viomycin 1 0 gm by intramuscular injection in the morning and again in the afternoon repeated every third day together with 12 gm of PAS daily (*b*) viomycin in the same dosage and pyrazinamide (see below) 20 to 30 mg per kg of body weight daily divided into three equal doses and taken by mouth after meals These regimens which are not very potent are not usually employed for periods of more than three or four months but they may be continued if there are no signs of toxicity The latter is sometimes prescribed during some critical situation such as the surgical resection of diseased pulmonary tissue from a patient whose tubercle bacilli are known or assumed to have become resistant to isoniazid streptomycin and para aminosalicylic acid during the previous course of treatment

Pyrazinamide inhibits the growth of tubercle bacilli of human origin but not bovine strains resistant strains are also found among wild colonies of the human type (Wasz Hockert and others 1956) Pyrazinamide was reported by its discoverers to have a tuberculostatic effect greater than that of PAS but less than that of streptomycin During treatment with pyrazinamide alone resistant strains of tubercle bacilli assume predominance relatively rapidly as compared with this phenomenon with respect to streptomycin or isoniazid a peculiar effect of pyrazinamide *in vitro* is the more rapid development of drug resistance when the medium is made acidic (Steenken and others 1957) Experimentally in diseased animals treatment with pyrazinamide together with isoniazid has been found highly efficacious but it has not been feasible to reproduce this advantage in human patients because of the toxicity of pyrazinamide in highly effective therapeutic doses (Muschenheim and others 1955) The restriction of daily dosage to the range of 20 to 30 mg per kg of body weight does not completely avoid the toxicity which is manifested commonly as hepatitis this may become evident clinically before the standard liver function tests deviate from the normal Usually the damaged liver heals itself when the drug is stopped but several fatal cases have been reported The effects of treatment therefore should be observed closely During the administration of pyrazinamide in daily doses of 3 0 gm the concentration of uric acid in the blood serum has been observed to rise to 9 mg per 100 ml and some of the patients develop symptoms of gout the effect appears to take place in the renal tubules (Cullen and others 1957) The abnormality rights itself when the drug is withdrawn from the regimen

Cycloserine is reported by Steenken and Wolinsky to inhibit the growth of human virulent strains of tubercle bacilli in concentrations of 6 25 micrograms per milliliter of liquid medium and 20 micrograms per cubic centimeter of soid medium horse serum in the medium decreases the susceptibility of the organisms They also found bovine and avian strains to be relatively less susceptible to the effects of the drug Except in monkeys cycloserine has no significant effect against tuberculosis in experimental animals (guinea pig mouse rabbit) a peculiarity which may be related to the very rapid elimination of the drug after its administration (Conzelman and Jones 1956) Cycloserine is active against tubercle bacilli which are resistant to the effects of streptomycin PAS or isoniazid During treatment with cycloserine alone strains of bacilli which are resistant to the effects of this drug appear in a relatively short time

In clinical practice cycloserine has been reported to be somewhat less effective against tuberculosis than streptomycin or isoniazid A limiting factor is the neurotoxicity of cycloserine which may be manifested in depressant or excitatory effects including somnolence convulsions mental and motor disorders (the latter may be epileptiform) dizziness and occasionally fever and chills Daily doses exceeding 25 mg per kg of body weight have been found to produce toxic reactions in almost all cases (Barclay and others 1957) Storey and McLean have summarized the experience and conclude that the convulsive effects are related to the total daily dose and to the size of the individual dose administered These effects are diminished or abolished if the total daily dose does not exceed 0 5 gm taken orally and the individual dose does not exceed 0 25 gm Likewise a total daily dose of 1 0 gm should

early adulthood and its subsequent preva lence seem to be related largely to constitu tional or endocrine influences causing in some people a lowering of resistance to the stress and strain of environment and to the more frequent acquisition of infection as people circulate more freely and widely in the community The onset of the disease at this time of life may be due to the exacerbation of old latent primary lesions or to the progression of those recently ac quired

The Early Lesion Characteristically the first recognizable lesion of tuberculosis of the lungs is parenchymal usually a bron chopneumonic focus which can be noticed in the roentgenogram because it casts a shadow approximately 1 0 cm more or less in diameter Before this size is at tained as Medlar has shown the lesion probably has undergone some caseation sloughing and local bronchial extension which may have occurred within a few weeks or months or perhaps at a much slower rate interrupted by periods of la tency or retrogression This inapparent evo lution is not apt to produce symptoms al though if it is a result of recently acquired primary infection the rather rare occur rence of *erythema nodosum* is sometimes reported Extension to the pleura may occur early even before the lesion is detectable on the roentgenogram followed by fibrinous or serofibrinous pleurisy

Progression of the Lesion The early le sion having already progressed unseen is likely to progress further especially in young patients If it does so it is usually by further caseation sloughing ulceration and bronchial dissemination The variety of progressions is infinite and only a few will be mentioned Most often the process is rather slow and there will be a series of small extensions of the disease in one or both lungs The clinical course is *insidious* As sloughing occurs into the bronchial tubes the purulent discharge mixes with bronchial mucus and the patient may have a slight cough usually in the mornings with scanty mucopurulent expectoration Examination of the sputum will often re veal the presence of tubercle bacilli After such ulceration bleeding may occur but in the early phases this seldom causes more than streaking" of the sputum The extensions in the lungs cause some toxicity but this too is not usually severe During a subsequent latency or even partial heal ing of the lesions these vague symptoms may all subside to add to the deception of the victim In such ways the disease may progress and subside from time to time until both lungs are widely involved

Acute Exacerbations Acute exacerbations of pulmonary tuberculosis are explained by similar mechanisms and are symptomati cally acute because of the suddenness and severity of bronchial dissemination The parenchymal focus after caseation and liquefaction may empty rather abruptly into the bronchial tree a quantity of pus highly charged with tubercle bacilli This is readily inhaled into healthy alveoli The irritating effects of the pus together with the massive infection give rise to an in tense inflammatory reaction manifested as subacute or *acute tuberculous pneumonia* usually of a confluent lobular distribution In some cases particularly in patients of low resistance this goes on to *acute caseous pneumonia* These acute forms are almost always related to a preexisting pulmonary lesion as stated but occasionally are caused by analogous mechanisms follow ing the rupture of a caseous tracheo bronchial lymph node into a bronchus The acute inflammation often produces profound toxicity Such exacerbations may follow within twenty four hours after a hemoptysis obviously explained by the inhalation of blood issuing from a cavity and washing tubercle bacilli with it This *acute post hemorrhagic tuberculous pneumonia* is usually in one or both lower lobes and may mark the transition from a limited disease with a single cavity into rapidly progres sive and fatal bilateral disease

Chronic Fibroid Lesions Chronic fibroid pulmonary tuberculosis is seen most often in elderly people whose lungs bear the scars of repeated battles with the bacillus The disease may have spread steadily but very slowly or in a series of exacerbations with long intervals of quiescence Areas of fibrosis may reflect good healing tendencies but as a rule there are other areas in which cavities and necrotic foci persist in spite of this With fibrosis goes emphysema pleural adhesions flattenings and immobili zations of the chest wall and retractions of the mediastinum Thus the elderly con sumptive may outlive his contemporaries

Onset of Pulmonary Tuberculosis As in dicated in the preceding paragraphs the mode of onset varies greatly according to the susceptibility of the patient and the behavior of the pulmonary lesions Com monly the first manifestations lag behind the actual appearance of the lesions and this *subclinical interval* may be short or long

Acute tuberculous pneumonia may pro

of regimens of drugs to be given concomitantly The combination of streptomycin 1 0 gm daily and isoniazid 200 mg daily is recognized by the British Research Council to be superior in most respects up to a period of three months If prolonged this regimen involves the possibility of developing bacterial resistance to both of these more potent drugs many physicians prefer holding one in reserve for possible future needs Also this dosage of streptomycin may be toxic for some patients and the isoniazid dosage is low by United States standards The usual isoniazid dosage in the United States is 300 to 400 mg each day or 5 to 6 mg of the drug per kg of body weight A regimen of isoniazid and PAS is well tolerated by most patients and in cavitary cases of pulmonary tuberculosis has been found somewhat more effective than a regimen of isoniazid daily and streptomycin twice weekly Streptomycin twice weekly and PAS daily is still less effective Kass and his co workers at the National Jewish Hospital (1957) espouse a concept based largely on the observations that certain antimicrobial drugs are most effective *in vitro* while tubercle bacilli are actively multiplying and that 8 to 16 mg of isoniazid per kg of body weight per day is desirable in most cases to ensure maintaining an adequate concentration of drug in the blood They found the most satisfactory regimen to be 15 to 30 mg of streptomycin per kg per day for ninety days or longer if the sputum still contained tubercle bacilli and the daily high isoniazid dosage for eighteen months thereafter Bed rest was not employed unless the patient was toxic This regimen has not yet been widely adopted mainly because of the satisfaction many have had with smaller doses

When resistance to isoniazid streptomycin and PAS or any two of them develops and the disease is not satisfactorily arrested recourse often has to be made to other regimens most of which are less potent and more limited because of their toxicity Examples of these second defense regimens are mentioned above

The use of *corticotropin* and *adrenocorticosteroids* in the therapy of tuberculosis has received increasing attention Early after the introduction of these hormones for the treatment of rheumatoid arthritis and other nontuberculous conditions reports of the aggravation or reactivation of accompanying tuberculosis usually in the lungs appeared Experimental evidence indicated that resistance to tuberculous as well as other infections may be lowered Further studies however have shown that this may not become manifest if such treatment is used only as an adjuvant of effective antituberculous chemotherapy Then the hormone effect may be strikingly and rapidly helpful Although the indications for the use of these hormones are not clearly defined they have been broadly outlined by the Committee on Therapy of the American Trudeau Society (1957) It is generally recommended that the hormones should not be used if satisfactory results can be expected with other treatment Situations in which they may be indicated include tuberculous meningitis with coma acute and advanced forms of pulmonary disease with overwhelming constitutional symptoms severe generalized miliary tuberculosis and severe and acute exudative involvement of the serous membranes and also in cases of severe and refractory hypersensitivity to the antituberculous drugs Quoting the report of the Committee

> The optimal duration of hormone therapy varies The usually recommended initial dose of 80 units of corticotropin gel 300 mg of cortisone per day or equivalent doses of corticotropin zinc hydrocortisone or prednisone should be reduced as early as possible but may be required for as long as two or three weeks It may be necessary to continue a smaller maintenance dose for three or four months or even longer The size of the maintenance dose should be the minimal amount necessary to maintain control as determined by frequent attempts at reduction of dosage

It is emphasized that the hormones should not be employed in cases in which the antituberculous therapy is known or suspected to be ineffective because of the presence of drug resistant strains of tubercle bacilli

TUBERCULOSIS OF THE LUNGS

Viewed in broad perspective pulmonary tuberculosis is the form dominating all others To epitomize the lung is the usual seat of the primary lesion and later if the primary heals of the reinfection lesion the pulmonary lesion is the common source of bronchial and other intracanalicular" dissemination of the infection and also of hemic dissemination leading to generalized disease Pulmonary tuberculosis is numerically far in the lead of all other forms as a cause of death epidemically the pulmonary lesion is paramount because it is usually the source from which the tubercle bacillus is passed through the community

Development and Clinical Course The rather abrupt rise in the occurrence of pulmonary tuberculosis in adolescence and

toxicity increases its effects become manifest earlier in the day and the patient may even notice that on awaking his vigor and energy are not restored In progressive disease the languor grows finally into a profound weakness and exhaustion

Loss of weight and impairment of tissue tone are also common At the true onset there may be no loss and a few patients even report gaining when their disease is first discovered The loss is usually gradual at first and may amount to only 4 or 5 pounds during several months Young people may fail merely to gain at the expected rate During acute and febrile phases the nutrition suffers much more rapidly and prominently

Cardiocirculatory instability is also a usual symptom and may persist long after the temperature becomes normal The usual manifestation is tachycardia the rate is regular and accelerated to 80 or 90 per minute during the early phases and subsequently may be higher After exertion or excitement the quickened rate does not subside as soon as might be expected The pulse is soft and the systolic blood pressure may be low frequently 90 to 100 mm of mercury The circulatory tone may be poor and the patient may complain of clamminess and coldness of the hands or feet the nails may be bluish Clubbing of the digits may never develop and only in advanced complicated cases is it occasionally extreme Malar flushing and other local thermic disturbances are related to fever and vagosympathetic reflexes

Digestive symptoms of a vague character are frequent and due particularly to the toxicity Severe distress such as dysphagia is not observed unless there is extensive tuberculous involvement of the larynx or pharynx Anorexia manifested as an indifference to food or a capriciousness of the appetite is frequent but usually corrects itself as the toxicity abates after which the patient even though confined to bed may eat heartily Vomiting is unusual unless the patient has advanced disease of the lungs and a harassing cough Intestinal symptoms such as seizures of colicky pain and diarrhea alternating with constipation strongly suggest an ulcerative lesion in the bowel as a secondary complication

The menarche may be delayed and menstruation may be irregular and scanty but as a rule this is observed only after disease is well established Amenorrhea is unusual except during the febrile stages The *fertility* of tuberculous women is somewhat impaired and in the advanced stages of the disease spontaneous abortion is un common A striking observation however is that chronically tuberculous women may bear a number of children There is little or no impairment of the sexual functions otherwise During the early and middle stages of the disease neither the *libido* nor *potentia coeundi* is appreciably reduced

Nervous and *psychic disturbances* are mild or entirely lacking In most of the early and moderately advanced and many of the far advanced cases there is no appreciable change and the patient s reactions are normal in the circumstances Later he may become rather neurotic *dependent introverted and depressed* (Schultz) This mood however is usually surprisingly mild considering the discouragement which such a chronic illness often entails Suicidal tendencies or attempts are most uncommon Euphoria which once was considered to characterize tuberculosis is not often noticeable except during the late or terminal stages *Toxic psychoses are rare*

Dyspnea is not usually an early symptom Slightly or moderately accelerated respiration may be noticeable during the febrile periods or in more advanced fibroid cases in which there is a good deal of secondary emphysema

Cough is the most common local symptom like others of this class seldom develops until the pulmonary lesion has broken down and ulcerated into the bronchi In the earlier stages cough is most pronounced when the patient awakes in the morning and is due to irritation of the bronchial mucosa from the accumulated discharges Occasionally cough is attributed to a reflex from irritation of the pleura and later it may be traced partly to tuberculous involvement of the larynx At first the symptom is usually slight and is quickly relieved after the small accumulation is cleared from the trachea and larynx Later especially if pulmonary excavation extends and the discharges increase the symptom may become troublesome interfering with eating and sleeping

Expectoration During the initial phases of the pulmonary infiltration there is seldom any expectoration except perhaps a little clear glary mucus Later however expectoration is a most common symptom Its quantity and frequency are variable Only a few particles of mucopurulent material may be brought up in the *morning* by clearing the throat or a few coughs gradually this may increase In other cases expectoration starts more abruptly and may

duce the first clinical symptoms This form is uncommon although not rare being ob served most often in young people in *Negroes and in debilitated old people* A preexisting excavating lesion is almost al ways present but the patient may not have been impressed with the mild symptoms caused by it The acute attack may appear to be precipitated by exposure to inclement weather by a common cold by severe sun *burn* by a hemoptysis or by some trivial influence The patient may experience chilliness prostration pain in the chest and fever this may rise quickly to 104° or 105° F and the pulse rate to 100 or more per minute The breathing is quickened at first (20 to 30 respirations per minute) *later becoming labored* and more rapid as the lungs become further engorged It is seldom noisy or grunting A feeling of con gestion in the chest increases and the lips and extremities become slightly or mode rately cyanotic The cough may not be severe at first and may be productive of *only a few milliliters of mucopurulent* sputum daily later larger quantities of a greenish yellow purulent character appear Unless hemoptysis occurred just before the onset the sputum usually is not bloody Because of the type of onset and the signs of lobar or lobular consolidation the pic ture may resemble closely that of a pneumo coccal infection (see Differential Diag nosis) Without proper treatment the course may be rapid ending fatally in two or three months in other cases it settles down to a subacute or chronic pace

More often the onset is attended by *grippe like symptoms* such as fever weak ness fatigue and mild aching in the mus cles which subside after a week or several weeks perhaps to recur at intervals when the patient again undertakes exertion In other cases and this is common there is an insidious unexplained slow loss of weight increasing fatigue and impairment of staying powers These symptoms con tinue for weeks or months before the pa tient is aware of serious difficulty then he may find an afternoon fever of a fraction of a degree to several degrees The usual rest does not restore his energies he finds his efficiency impaired and he is puzzled by his inability to concentrate on his work Other patients are disturbed by some par ticular constitutional symptoms such as *sweating* at night *amenorrhea* or *anorexia* and *indigestion* *Under any of these condi* tions it is learned usually that the patient previously has had some *cough* and *expec toration* or at least a clearing of the throat in the morning Sometimes he will report that there has been a little blood in the sputum at irregular intervals In other in stances *hemoptysis* may be the initial symptom so far as the patient is subjec tively aware and this may consist only of a few spots or streaks of blood in the sputum or free and profuse bleeding He may find a small amount of blood accumu lated in his throat upon awaking in the morning *Pleurisy* may cause the outstand ing initial symptom of characteristic sharp pain (see Tuberculosis of the Pleura)

Hoarseness dryness and tickling in the throat or other symptoms of acute or chronic *laryngitis* may be the first to arrest attention Likewise the pain or discharge of a perianal abscess may be the chief com plaint the mild pulmonary symptoms pre viously having been ignored

Symptoms of Pulmonary Tuberculosis *Fever* Usually the temperature is normal or subnormal in the morning the rectal read ing sometimes being as low as 96 5° or 97° F *and there may be considerable prostra* tion and weakness Between 4 00 and 8 00 P M the fever reaches its height which in acute cases may be 105 or 106° F More commonly in subacute or mild cases it ranges up to two or three degrees above normal Usually a low or moderate fever recurs each afternoon or evening for some days or weeks and in the advanced case this may continue for many months Dur ing grippelike episodes the temperature may rise to *103° or 104° F daily for a week* or so then gradually subside by lysis until it is normal after several weeks

Chilliness is sometimes a complaint as sociated with a temperature of 103° to 105 F especially if this appears suddenly

Sweating is not a feature of early tuber culosis and is not often a symptom except in the febrile and exhausted states Then it occurs usually at the time of the tem perature rise and immediately afterward *In some cases in which there is extensive* excavation of the lungs and secondary suppurative infection the sweats are drenching and prostrating

Malaise lassitude and *fatigue* are the most common symptoms of tuberculous toxicity At first they are noticed toward the end of the day s activity when the patient may eschew his usual diversions or interests in order to get additional rest If he is the type to disregard such mild symp- toms he may become irritable grouchy and impatient However the symptoms are not always unpleasant and may be evidenced only as an urge to rest and sleep If the

Wheezing and stridulous breathing are occasionally complaints in cases of cavernous tuberculosis less often in others The *wheezing may be noticeable behind the* sternum but more often is localized to one side of the chest and is due usually to distortions or stenosis of the bronchus or trachea caused by tuberculous ulceration granulomas or cicatrices Rarely the trachea becomes so filled with edematous inflammatory tissue that suffocative attacks may occur In old standing fibroid cases wheezing may be referable to catarrhal accumulations in distorted bronchial tubes

Hoarseness may be the result of temporary congestion of the larynx from incessant coughing Persistent hoarseness dryness and tickling of the throat are caused often by laryngeal tuberculosis

Physical and Roentgenographic Examination in Pulmonary Tuberculosis The physical examination of a patient for pulmonary *tuberculosis should be thorough and com*plete Fluoroscopy is useful and sufficient to visualize changes in respiratory mechanics and gross densities in the lungs However the greater accuracy of the roentgenogram must be appreciated particularly in detecting early lesions

Physical Examination of the Patient with Limited or Early Pulmonary Tuberculosis In the case of a relatively early lesion physical examination reveals no superficial abnormalities or perhaps only slight evidence of anemia and loss of weight The temperature may be found normal or elevated a fraction of a degree to several degrees and the pulse may be moderately accelerated Careful examination of the chest may not reveal abnormal signs or one may detect definite changes such as slight dullness bronchovesicular breathing and a few persistent crepitant or moderately coarse rales Rales alone may be found in an area scarcely more than 1 0 or 2 0 cm in diameter The roentgenogram as a rule reveals evidence of the lesion more precisely as a soft cloudy mottling often associated with small honeycombed areas of rarefaction or larger round zones of similar translucency which represent cavities (see Fig 29) In*frequently in the case of a small tubercu*lous lesion the roentgenographic findings are negative or indeterminate while definite rales may be heard in a given spot Oblique roentgenographic views or other *special views then may reveal the mottling* or rarefaction which in the customary posteroanterior view was concealed by the interposed density of the heart or some other structure These evidences of the lesions are usually disclosed in the upper third of one lung not infrequently beneath the level of the clavicle but sometimes ex*clusively above it Signs of similar or differ*ent intensity and variety may be detected sometimes in both lungs These may be located on one side in the upper third and at the apex of the opposite lung or there may be other variations such as apical signs on one side and basal signs in either one of the lower lobes In a few cases the signs are limited to the middle or lower part of the interscapular region on one side occasionally even below this level In some the original apical lesion is so slight as to give no definite signs either by physical or roentgenographic examination while the obviously secondary lesions are easily detected

Long standing and fibroid lesions may betray their presence through the changes due to retraction and shrinkage of the *fibrous tissue Thus a rather limited de*pression of the clavicular fossae on one side slight or moderate atrophy of the muscles in this region limitation of motion of the ribs and deflection of the trachea give the main clue to the long duration of the lesion Isolated nodular fibrotic or calcified lesions such as those of the primary complex usually are not detected by physical examination but cast characteristic dense sharply circumscribed shadows in the roentgenogram

Physical and Roentgenographic Signs of



Fig 29 Recently developed tuberculous lesion in right lung motheaten appearance of density in second anterior interspace suggests softening and excavation

soon amount to one ounce or so in a day In any case with progressive pulmonary excavation the quantity usually increases until 30 or 60 ml are produced each day mainly in the morning In advanced cases 300 to 350 ml may be brought up daily The sputum is not foul except in the unusual case in which secondary anaerobic infection develops in the bronchi or pulmonary cavities When expectoration is slight the flecks of pus are seen in the clear mucus In caseous pneumonic cases particularly at the start of excavation the sputum is purulent and of a greenish yellow color but later this usually becomes yellow and the admixture of mucus is noted In more chronic cases the mucopurulent material is of a coherent sometimes tenacious character The sputum on standing retains its homogeneous mucopurulent character and does not separate into layers The quantity and the character of the expectoration reflect to some extent the changes occurring in the pulmonary lesions A daily production of 30 to 60 ml of purulent green matter speaks for a caseous pneumonic liquefying lesion A change to yellowish more mucoid sputum suggests a subsidence of the ulcerative process indicated further by a diminution of the amount and a continuing decrease of the purulent element Sudden and marked variations in the quantity of the sputum may be due to bronchial occlusion

Hemoptysis Blood spitting occurs in more than one half of all cases of untreated pulmonary tuberculosis As a rule the quantity is small consisting of streaking spotting or pinkishness of the sputum in the mornings but copious bleeding is not rare Hemoptysis usually is due to the ulceration or weakening and rupture of the walls of the vessels in tuberculosis cavities Infrequently in chronic healed cases it may be traced to the mechanical rupture of superficial vessels in the walls of distorted bronchi An ulcerative lesion in the trachea or bronchus also is an infrequent cause As a rule the symptom is obviously not an indication of early disease Bleeding may start at any time during the day or night but has been observed more frequently in the early hours of the morning Exceptionally it is induced by a violent straining effort or by trauma Staining or streaking of the sputum may occur without other sequels but in other cases is a precursor of more copious hemoptyses Frank hemoptyses however appear most often without forewarning In women there may be a definite relationship with menstruation and a few have recurrent hemoptyses monthly During the bleeding the patient may notice boiling or bubbling sounds in his chest localized to one side or to the center The blood may be raised easily or may flow so freely as to cause severe choking coughing and gagging

Immediately fatal hemoptyses occur only in a small minority of the cases usually of longstanding fibroid cavernous tuberculosis in which vascular granulation and connective tissue have proliferated in the cavity walls a vessel may undergo gradual aneurysmal dilatation (Rasmussen) until it finally gives way As a rule however a single hemoptysis amounts to 30 or 60 ml occasionally to as much as 300 ml The bleeding is then usually arrested by the deposition of a clot at the site of the vascular rupture Dark clots may be expectorated for several days sometimes in the form of bronchial casts This may be the end of it but there may be a few or many recurrences at intervals of hours days or longer periods Then the loss of blood may cause anemia The patient may become nervous and frightened or may go into mild shock with fearfuness pallor coldness of the extremities tachycardia and weakness and sometimes sweating Vomiting may occur soon after especially if the patient has swallowed much blood Within a day or two there may be a rise in temperature of several degrees usually traceable to the aspiration of blood into the lower lobes of the lungs The resulting tuberculous pneumonia has been described in pervious paragraphs

Pain in the chest is usually a symptom of inflamed pleura It may be an early complaint therefore if the initial pulmonary infiltration is situated close beneath the pleura facilitating such secondary extension In cases associated with chronic adhesive pleurisy a dullness heaviness soreness and aching of the side is a common complaint and is particularly noticeable during fatigue and during cold damp weather Such sensations may be noticeable for many years after all activity of the lesions has subsided A sudden stabbing pain in one side or behind the sternum followed immediately by shortness of breath and other manifestations is usually indicative of collapse of the lung and acute pneumothorax Persistent or recurrent localized pain may be referable to tuberculous lesions of the spine costal cartilage or sternum less often of the ribs or sternoclavicular joints these may be associated with superficial swelling and redness

Blood Cell counts estimation of the hemoglobin and the erythrocyte sedimentation rate are used routinely in clinical practice Interpreted in combination with other data they are valuable in diagnosis and in following the course of the disease (See Changes in the Blood of Tuberculous Patients p 254)

Urine In febrile tuberculosis the urine commonly shows slight traces of albumin Protein loss through the kidney may become marked after amyloid changes have occurred From the results of animal experimentation it has been suggested that tubercle bacilli free in the blood stream may be excreted through the intact and normal kidney and then may be discovered in the urine (excretory bacilluria) In human beings however experience indicates that this must be a rare happening and the discovery of bacilluria is taken as presumptive evidence of a tuberculous lesion in the urinary tract or the genital organs The discovery of pus cells and an abnormal number of erythrocytes or persistent albuminuria in a patient with pulmonary tuberculosis should always lead to a further investigation for the presence of a renal lesion

Pleural Fluid In some cases of pulmonary tuberculosis complicated by a pleural effusion the discovery of tubercle bacilli in the aspirated fluid may verify the diagnosis when this evidence is lacking on account of negative tests of the sputum

Basal Metabolic Rate In afebrile cases of pulmonary tuberculosis this is normal unless there is some independent cause for variation In febrile cases the rate is elevated according to the degree of fever

Respiratory Function In the presence of limited lesions the respiratory function is not materially disturbed In later stages functional impairment may become severe because of the invasion and destruction of pulmonary parenchyma and shrinkage of fibrous tissue in the lung and the pleura and the associated retraction of the heart and distortion of bronchi and blood vessels Secondary emphysema may also be a serious functional handicap The degree and significance of the impairment may be determined with considerable accuracy by the separate measurement of ventilation the mixing of gases in the lungs the adequacy of exchange of gases between the alveoli and the pulmonary capillaries and the efficiency of the pulmonary circulation By using the bronchospirometer some of these measurements can be made separately for each lung The tests are needed in certain cases to help determine the patient s probable tolerance of surgical procedures such as pulmonary resection

Diagnosis of Pulmonary Tuberculosis Tuberculosis should be considered as a possible cause (*a*) in any patient who presents vague symptoms of loss of weight malaise and easy fatigue particularly when this is associated with persistent cough (*b*) in any patient particularly a young person who has recurrent or prolonged attacks simulating grippe or influenza (*c*) in any patient who has atypical or unresolved pneumonia (*d*) in any patient who has cough and expectoration persisting for more than several weeks even though there may be little or no impairment of the general condition (*e*) in any patient who spits blood (*f*) in any patient who has pleurisy especially with effusion (*g*) in any patient with a persistent unexplained fever (*h*) in any patient with other mild or obscure lesions such as persistent lymphadenopathy fistula in ano and chronic laryngitis giving rise to chronic hoarseness The diagnosis then depends particularly upon physical roentgenographic and laboratory examinations In such circumstances the finding of a lesion usually in the upper half of the lung which gives the characteristic roentgenographic appearance of an infiltration or fibrosis with or without cavity and with or without demonstrable physical signs such as rales warrants the presumptive diagnosis of tuberculosis If there is no demonstrable cavity and no sputum the diagnosis is confirmed by a period of observation during which the lesion persists or gradually changes cultures of gastric fluid may grow tubercle bacilli If excavation is demonstrated or suggested by the other examinations the diagnosis should be verified by the finding of tubercle bacilli in the sputum The failure to find bacilli in a case in which there is moderate or fairly copious mucopurulent sputum weighs heavily against the diagnosis of tuberculosis The finding of tubercle bacilli in the discharges or material obtained from other lesions such as pleural effusion or pus from a tuberculous fistula strongly suggest that the pulmonary lesions are also tuberculous The finding of rales in the upper third of the chest in a case in which the roentgenogram shows no parenchymal change and in which the sputum test is negative for tubercle bacilli leaves the diagnosis in doubt and raises the question whether the lesion is nontuberculous The finding of physical and roentgenographic signs exclu

Advanced Lesions in Pulmonary Tuberculosis There is no limit to the variety of signs which may be produced by extensive tuberculosis If the disease remains confined chiefly to one lung this may be converted into a fibrous shrunken mass with a variety of secondary effects such as flattening and immobilization of the hemithorax atrophy of the muscles and skin on this side inequality of the pupils from involvement of the sympathetic ganglia flushing of one cheek from a similar cause dilated superficial venules of the skin of the chest marked deflection of the trachea and retraction of the heart The roentgenogram may show a shrunken and opaque lung and the retractions associated with it while physical examination may reveal dullness to flatness bronchial and amphoric breathing post tussic suction widely distributed rales and many other classic signs In the case of advanced bilateral fibroid nodular tuberculosis secondary emphysema may be conspicuous and the physical signs of this together with few rales may leave one in doubt until the roentgenogram shows the typical distribution of nodular and streaky shadows throughout both lung fields

Extensive bronchopneumonic or pneumonic lesions which have not existed long enough to produce such secondary changes give rise most constantly to widely distributed rales which vary from the crepitant quality in the early stages of infiltration to moderately coarse bubbling and consonating rales after the lesions have caseated and undergone liquefaction and ulceration With these are discovered varying signs of solidification and excavation depending on the concentration of the lesions in a given lobe and their state of degeneration Physical signs then may be more informative than the roentgenogram since in the latter the opacity may be so complete that detailed structure can no longer be made out Smaller bronchopneumonic lesions however are usually depicted more faithfully by roentgenographic than by physical signs In all these situations the findings may be associated with or modified by changes in the pleura or other adjacent structures A large pleural effusion may obscure pulmonary lesions while more chronic pleura changes may be well revealed by peripheral densities and retractions which stand out in contrast with the air bearing lung

Tomograms (planigrams laminograms selectoplanes) are helpful to supplement conventional roentgenograms especially in defining more precisely the composition and location of individual lesions

Complete examination of the body may also bring to light changes outside the thorax Thus the discovery of an inflammatory thickening of one vocal cord of a phlyctenule in the conjunctiva of a nodule in the epididymis or of a fistula in ano may be most important factors in constructing the complete picture of the disease

Laboratory Findings in Pulmonary Tuberculosis *Sputum* Proper collection and examination of the sputum are most important There may be none if the pulmonary lesion has not ulcerated Even after ulceration has occurred the quantity of discharge may be so small that the patient is not aware of it and unconsciously may swallow it In this case he is carefully instructed to collect in a suitable container any slight discharge appearing in the throat particularly in the mornings If he is unable to produce a satisfactory specimen the *fasting stomach contents* are aspirated with a stomach tube when the patient first awakes in the morning This specimen is treated by centrifugation neutralization and inoculation on suitable cultural medium *Laryngeal smears* have been used to recover small mucopurulent discharges for examination this is quick and convenient but not to be relied upon if no acid fast organisms are demonstrated *Bronchial lavage* (introducing 20 ml of warm saline solution into the trachea and then collecting the expectorated material for examination) has been advocated but is not to be recommended because of the hazard of bronchial dissemination of the infection Occasionally bronchoscopic specimens contain demonstrable bacilli when expectorated material does not Organisms may also be found in the feces

Ordinarily the patient with a pulmonary cavity will be able to collect mucopurulent material upon awaking in the morning and this is the specimen needed Occasionally bloody specimens or the blood from a hemoptysis will be suitable for examination A great many elements may be searched for such as elastic fibers various types of cells secondary organisms and albumin but these have only subsidiary value unless some special point is to be determined The most important items are an estimate of the character and daily volume of the sputum and an effort to detect tubercle bacilli in it (See Demonstrating the Tubercle Bacilli p 253) Appearance consistency possible layering and odor are noted

usually can be made in the space of a relatively few days Acute bronchopneumonia due to organisms such as *streptococci* or *anaerobic bacteria* which commonly goes on to abscess formation may be confusing because of the pattern of the pulmonary lesions simulating tuberculosis The acute onset often with chills the leukocytosis the finding of an abscess or cavity and the failure to demonstrate tubercle bacilli in the sputum are presumptive evidence against the tuberculous nature of the disease while a great predominance of other specific organisms may give the real clue One must be certain however that common pyogenic organisms are not merely contaminants from the mouth

Foulness of the sputum shortly after the acute onset of the disease always speaks for *putrid lung abscess* In longstanding cases of chronic lung abscess a cavity or fibrotic lesion may be discovered in the upper part of one lung and this may give rise to suggestive symptoms such as hemoptysis The history of onset particularly the history of fetid expectoration and the failure to demonstrate tubercle bacilli usually indicate the diagnosis

When tuberculosis is suspected as the cause of a *protracted and obscure fever* the failure to find a pulmonary lesion is presumptive evidence against this diagnosis but it may be necessary still to exclude the presence of tuberculosis of other organs The same is true in any chronic debilitated state in which tuberculosis may be suspected

Bronchiectasis not infrequently must be differentiated in patients who give a history of chronic cough possibly with foul and bloody sputum The lesion is usually in the lower lobes but occasionally is apical Rales may be heard but the roentgenogram fails to show the typical tuberculous infiltration and excavation and instead there may only be strandlike densities suggesting interstitial or peribronchial fibrosis This and the absence of tubercle bacilli from the sputum suggest bronchiectasis which may be verified by the use of bronchography with iodized oil

Cancer of the lung simulates tuberculosis because of the chronic cough expectoration of pus and blood febrile episodes and gradual wasting Physical and roentgenographic findings are more likely to be those of a bronchial lesion causing localized wheezing rhonchi or of suppurative pneumonia secondary to the bronchial occlusion The failure to find tubercle bacilli in the purulent sputum is most important Bronchoscopy the biopsy of a superficial metastatic lesion in a lymph node or the finding of other internal metastases may be diagnostic

Special cytological studies may reveal cancer cells in the sputum and this may be a crucial finding in the case of peripheral roentgenographically spherical lesions too distant to be reached by the bronchoscope Such a density on the roentgenogram is also consistent with some benign tumors and with certain caseous or fibrocaseous lesions ("tuberculoma") In doubtful cases of potentially serious import surgical exploration by thoracotomy may be indicated

Pulmonary fibrosis and *emphysema* may have to be differentiated because of symptoms and because tuberculosis particularly the chronic disseminated form sometimes is a cause Chronic cough occasional blood spitting and increasing weakness may be particularly suggestive In tuberculosis the fibrous changes are usually associated with calcifications identified by roentgenography Extrapulmonary lesions may also be found especially in the lymphatic system or in the abdomen The history of some other possible cause such as chronic paranasal sinusitis or exposure to injurious dust may give the proper clue In *silicosis* the nodular noncalcareous roentgenographic appearance of the lesions evenly distributed in both lungs particularly in the central portions is characteristic Association of tuberculosis with silicosis a not infrequent finding may be suspected when there are confluent roentgenographic shadows in addition to nodular ones

There is a sizable category of nodular and stringy lesions revealed best in the roentgenogram which may simulate tuberculosis of a disseminated distribution particularly that due to hemic dissemination In addition to silicosis this group includes sarcoidosis metastatic carcinosis and unusual or rare lesions such as the pulmonary granulomatosis of beryllium workers and those associated with scleroderma tuberous sclerosis and primary amyloidosis Chronic pneumonia due to the inhalation of mineral or other oils may give a confusing picture but is more likely to be unilateral confluent and limited than widespread

Mycoses may produce changes simulating tuberculosis but these are unusual The lesions may be of a subacute bronchopneumonic or chronic granulomatous and fibrous nature and the pattern in the roentgenogram may simulate tuberculosis closely even to cavity formation In a pa



Fig 30 Tuberculous cavity in the right lower lobe at the level of the eighth rib posteriorly Exudative infiltrate in the middle of the left lung represents a bronchogenic extension from the cavity

sively in the lower half of the chest does not exclude tuberculosis as a cause but if in addition there is mucopurulent sputum devoid of tubercle bacilli tuberculosis as a rule can be excluded In doubtful or difficult cases the tuberculin test may be valuable especially if negative

Modern *methods of tuberculosis case finding* among apparently healthy people afford another approach Among each group of 1000 adults thirty years of age or older routine roentgenographic examination of the lungs reveals active tuberculosis in one or two individuals the rate is even higher in certain groups such as elderly people admitted to hospitals for the treatment of some other condition Because of the lower incidence of tuberculous infection among young people especially children and the desirability of avoiding unnecessary exposure to radiation at this time of life tuberculin testing is recommended The chests of positive reactors then should be examined by roentgenograms and if necessary by other procedures as well Among "negatives no further examination is usually necessary although it is advisable to repeat the tuberculin test at intervals of a year or two to detect the possible acquisition of a primary infection Aside from the finding of obviously active disease many adults (1 0 or 2 0 per cent) will be discovered bearing pulmonary lesions due apparently to inactive tuberculosis or to some other cause Some of these require study to determine the import of the lesions and the correct etiological diagnosis

Differential Diagnosis of Pulmonary Tuberculosis The approach to differential diagnosis varies according to the presenting findings Thorough and careful study of the case usually enables one to arrive at a definite conclusion

In a patient in whom unexplained fever develops and who is discovered to have a pneumonic lesion without demonstrable excavation distinction often has to be made between *early tuberculosis and simple bronchopneumonia* especially if the lesion is confined to an upper lobe Demonstrably rapid changes in the lesions within a few days or a week and failure to find tubercle bacilli usually identify bronchopneumonia as such while the failure of the lesion to clear in the expected time favors tuberculosis Similar distinctions are of value in the differentiation of *eosinophilic infiltrates of the lung sometimes representing bronchopneumonia* in a patient who gives a history of asthma or other allergy the eosinophils of the blood may rise to 25 per cent or more of the leukocytes

In *viral pneumonia* the pulmonary lesions sometimes may fail to resolve completely before several months have elapsed as indicated by persistent shadows on the roentgenogram and rales The acute onset and course the absence of pulmonary cavity the failure to demonstrate tubercle bacilli and the gradual and complete resolution of the lesions even if delayed exclude tuberculosis Occasionally acute caseous pneumonia occupying a large part of the lobe or lung may be confused with *pneumococcal lobar pneumonia* and the confusion may be increased by the finding of pneumococci of a higher type in the sputum While in a rare case of tuberculous pneumonia the leukocytes of the blood may rise to 20 000 per cu mm the count seldom attains the height commonly seen in lobar pneumonia nor is there often such a pronounced relative increase of the polymorphonuclear neutrophils Since caseous pneumonia usually represents an acute confluent bronchopneumonic extension from a tuberculous cavity tubercle bacilli will be found on careful search of the sputum which as a rule is not rusty although it may be bloody In caseous pneumonia the signs of cavity may be detected on physical and roentgenographic examinations If not immediately the diagnosis

most always do well under suitable treatment In such cases the life expectancy is equal almost to that of groups of similar age in the general population The more extensive the pulmonary lesions the greater is the future hazard Before the advent of chemotherapy patients with far advanced cavitary disease had an average life expectancy of two to five years and about a third of those in the moderately advanced stage were dead within five years Chemotherapy has vastly improved the lot of such patients in prolonging life and raising the chances of satisfactory arrest of the disease However such benefits are far outweighed by the advantages of an early diagnosis

Under treatment which includes appropriate chemotherapy it is only the exceptional patient who does not show some favorable response The subsidence of symptoms is often rapid and striking and the early resolution of the exudative inflammatory components of the lesions may be most impressive A state of well being may be achieved rather soon and this can be deceptive—the false recovery" which was recognized by Laennec and many who followed him At this point and later the crux of the prognosis rests in the expected persistence in the body of living tubercle bacilli the likelihood of their permanent confinement anatomically and the biological factors of vital resistance which when sufficient restrain or prevent bacterial multiplication and thus avoid a recrudescence of the disease The multiplicity of choices of regimens of chemotherapy which are now available and the avenues of management which these have opened through the medium of surgical resection and other manipulations have completely changed the view of prognosis Formerly this was based on extensive statistics relating largely to the natural course of the disease and pointing to the grim conclusion that while the course could often be slowed or halted by rest treatment and a mode of life keyed to the handicap eventual death from slow progression or final flare up was to be expected in most cases Even then however the prognosis of the minimal case detected early after its inception and treated with understanding and care was excellent Today many of those ominous clinical portents of a decade ago need not hold Swift death from meningitis generalized miliary disease and *phthisis florida* can be averted and the possibility of permanently arresting pulmonary cases has been vastly extended Already many recovered or improved patients formerly rated as lost have lived to die from other unrelated causes while some have succumbed to the syndrome of cor pulmonale because of the remarkable scarring of extensively diseased lungs Although sufficient time has not yet elapsed to determine the rate of relapse and the final outcome of many cases treated by current methods certain factors may be mentioned which have an important influence

The *character and pathological anatomy of the lesions* are of great significance Accumulations of inflammatory exudate which have not undergone necrosis are capable of resolution and this is observed in most cases of pneumonic tuberculosis However these are almost always a part of a lesion which is necrotic and caseous at or near its center the latter generally is incapable of resolving and constitutes much or most of the residual lesion after resolution has been completed Tubercle bacilli usually disappear from the areas in which resolution has occurred but they survive in necrotic areas of caseation abscess and cavitation healing then depends mainly on fibrosis In the lungs single or several isolated caseous residues of 1 0 or 2 0 cm in diameter usually become more or less encapsulated with fibrous tissue under continued chemotherapy and the rate of relapse up to five years appears to be less than 5 per cent Larger lesions of this type are more liable later to liquefaction and excavation leading to an exacerbation of the disease and this is particularly true of massive caseous pneumonia Pulmonary cavities several centimeters in diameter frequently become dry and relatively clean and then under continuing chemotherapy may be closed by the shrinkage of fibrous tissue laid down in the walls Tubercle bacilli disappear from the sputum (the "closed negative case) and the outlook for permanency of healing is excellent Large cavities usually do not close completely As they persist some may continue discharging tubercle bacilli (the open positive" case) a sign of active infection threatening progressive invasion of the lungs others dry out as the walls are partly transformed into fibrous tissue and tubercle bacilli are no longer demonstrable in the sputum (the open negative case) Among 475 patients followed up to five years and reported by J W Raleigh (1957) the relapse rate in the "closed negative" cases was about 18 per cent in the open negative about 40 per cent The open negative case is a unique product of chemotherapy since before its advent a

tient suffering with a chronic cough ex pectoration and general ill health failure to demonstrate tubercle bacilli and the finding of specific fungi in the sputum by microscopic or cultural examinations may settle the diagnosis other tests used include the serum antibody titer skin sensitivity tests and virulence of the organisms for animals It is important to know whether there has been an opportunity for infection with fungi and whether there have been systemic lesions

In the desert section of southwestern United States infection with *Coccidioides immitis* is fairly common and in a few of those infected acute pneumonic lesions develop some with excavation In less than 1 per cent of those infected the disease becomes generalized and fatal The coccidioidin skin test serological and bacteriological findings and the usually short clinical course are diagnostic features *Histoplasmosis* also has been identified as a cause of chronic pulmonary lesions which may be followed by calcification particularly in the eastern central part of the United States Testing with histoplasmin for sensitivity of the skin and the use of the specific complement fixation test are important aids in diagnosis Other mycoses found more often in rural than in urban populations which may involve the lungs and simulate tuberculosis include actinomycosis blastomycosis and cryptococcosis It is always important when fungi are found in the sputum to determine whether these are implicated in the pulmonary disease or are merely nonpathogenic inhabitants of the mouth In the great majority of cases the diagnosis uncertain at first resolves itself into that of tuberculosis

Since in the United States and many other countries tuberculous infection early in life is no longer almost a universal phenomenon the value of the tuberculin skin test as an easy and reliable aid in differential diagnosis has been greatly enhanced in most questionable cases a negative test affords strong evidence against tuberculosis In the presence of etiologically obscure pulmonary disease which appears to be clearly or possibly of a disseminated or chronic infiltrative or granulomatous nature it is customary now in some areas to perform the tuberculin test simultaneously with the coccidioidin and histoplasmin tests in the hope of expediting the diagnosis In more difficult and urgent situations the examination of specimens removed by biopsy from tributary lymph nodes the liver the bone marrow or even from the lung itself may be indicated

Pulmonary lesions secondary to cardiac disease sometimes create a confusing picture The hemoptysis of mitral stenosis may be misleading at first because of the finding of rales and roentgenographic changes suggesting fibrosis and infiltration of the parenchyma Demonstration of the cardiac lesion the failure to demonstrate a cavity the lack of sputum containing tubercle bacilli and the distribution character and behavior of the lesions lead correctly to the conclusion that the lesions are due to secondary fibrosis from congestion and stasis (associated in exceptional cases with *hemosiderosis*) or to infarction or edema A pleural effusion clouding the picture may be found related to the same cause Rarely a pulmonary *infarct* may become secondarily infected and break down to form an abscess simulating a tuberculous cavity

Suppurative lesions in other structures which may become connected with the lungs must be distinguished Thus chronic pleural empyema which has ruptured into the lung may cause many symptoms common to pulmonary tuberculosis and the same may be said of chronic hepatic or subphrenic abscess which has perforated through the diaphragm into the lung A searching history of previous illnesses and operations and failure to demonstrate tubercle bacilli in the sputum usually eliminate tuberculosis

Unusual conditions such as Hodgkin s lymphoblastoma invading the lung from the mediastinum esophagotracheal fistula dermoid or parasitic cysts which have ruptured into the lung and aortic aneurysm producing bronchial stenosis by pressure may necessitate excluding tuberculosis because of the symptoms of chronic pulmonary disease The clinical history the failure to find tubercle bacilli and the demonstration of other lesions especially in the mediastinum exclude tuberculosis as a rule and suggest the proper diagnosis

Prognosis of Pulmonary Tuberculosis A favorable outcome is best assured by the detection of the disease in its early phases the administration of proper treatment and the continuation of this procedure until healing processes are well established and a solid balance of vital resistance can be assumed to exist There is a definite correlation between the *extent of the lesions* and the ultimate prognosis Early "minimal lesions without cavity formation al

tion once every six to twelve months to detect possible instability Others of less certain status especially if the lesions are suspected to be poorly fibrosed partly necrotic and possibly honeycombed with minute cavities should be studied more thoroughly with all available diagnostic procedures including cultures of the sputum and gastric fluid to determine whether active treatment is needed Some of these patients benefit by a period of hospitalization for this intensive study This may clarify the situation and justify allowing some to continue an active life under the watchful eye of a physician Others who have vague symptoms of undue fatigue and loss of weight may be assumed sometimes to suffer mild toxicity from partly healed but unstable pulmonary disease and they may benefit from a period of treatment such a precaution may prevent more serious exacerbations Some too may have such symptoms from disease in other organs while the pulmonary lesions remain inactive treatment may be indicated on this account

There is also a group of patients who seem to have developed fairly good resistance and who have unawaredly coped with the disease with some success before a diagnosis is made Many of these will be found to have partially fibroid lesions containing small cavities and mild symptoms including scanty expectoration containing tubercle bacilli Trouble is brewing for these patients and their management demands careful judgment An elderly person may maintain the balance in his favor by limiting his activities under medical treatment but a younger one should have the benefit of more active and radical treatment in view of the prospect of permanent recovery

Patients with advanced bilateral cavitary disease can be helped at least temporarily with prolonged chemotherapy Although they have chronic permanently disabling disease to which most of them eventually succumb their lives often may be prolonged and made more comfortable

Principles Objectives and Methods of Treatment Recognizing that tuberculosis of sufficient extent and activity to require treatment has already caused some necrosis and possible excavation of tissue it is appreciated from the start that treatment is a long term proposition Fairly rapid resolution of exudative lesions may be promoted but the fibrous repair of necrotic residuals requires many months Since there is no proof that infection can be completely eliminated by the use of drugs or other measures the possibility of later recrudescence of the disease must always be considered and treatment should be planned with the aim of averting this Much time is required not only for fibrous healing of lesions but also to raise the patient s resistance to the infection to the highest possible level When the diagnosis is made it may be possible to judge approximately the kinds of treatment which are likely to be most effective and to anticipate the probable outcome However the response varies from one patient to another and valuable information is gained by observing the effects of a chosen regimen during the early weeks and months In time it is learned for instance whether acute tuberculous pneumonia is to undergo extensive resolution or whether widespread necrosis prevents this and points to the eventual need of surgical resection Similarly during the early course small exudative lesions in one lung may resolve almost completely leaving a major problem of advanced fibrocavitary disease in the opposite lung which may have to be treated by surgical collapse or resection At the start the probable duration of treatment though very important to the patient is secondary to a consideration of the result which eventually it is hoped to achieve

The first objective is to suppress microbial activity and halt the progress of the disease as quickly as possible and especially to stop the destruction of tissue Once this is achieved fibrous repair can proceed at its maximal rate All reasonable and necessary measures therefore are adopted Although in many instances rest treatment alone or chemotherapy alone may act favorably—the former by allowing the natural defenses to function best and the latter by its specific antimicrobial effect—the results are likely to be better if at the start both are employed The choice and dosage of drugs may vary somewhat according to the severity of the disease and are relied upon heavily to control the infection Until this is accomplished in the more active cases as indicated by a material reduction of the cough and expectoration and a lowering of fever the patient is kept in bed and given nursing care Once the symptoms of active infection have subsided and the beginning resolution of the pulmonary lesions is demonstrated it is usually safe to permit him a few liberties such as sitting out of bed for meals and walking to the bathroom and these may be gradually increased The time for such steps varies greatly In the acute caseous pneumonic cases several months may pass before the

cavity was virtually synonymous with positive sputum The formerly poor prognosis signalled by a persisting cavity has been greatly improved but obviously by no means reversed

The principles implicit in this discussion apply also in other lesions Ulcers of the skin larynx intestine or bladder usually heal durably under chemotherapy partly a credit to their superficial location and the absence of deep enclosed necrotic masses On the other hand caseous residues of material size in such structures as bone kidney and fallopian tubes may be smoldering foci which stimulate the formation of fibrous tissue in their environs and may flare up from time to time Meanwhile under chemotherapy the caseous matter may become inspissated at least temporarily and sinuses leading to the surface from underlying abscesses may close and heal

Relapse when it occurs is almost always related to an exacerbation in one or more of these necrotic residues and the risk depending on so many factors is difficult to forecast The stress and strain of life operating in devious and largely obscure ways have long been recognized as strong influences Heavy labor aside from the deleterious effects of attendant excessive fatigue may in a mechanical way stimulate a quickened circulation of blood and lymph in and about a lesion and thus favor its reactivation liquefaction and extension By way of contrast patients leading a closely sheltered strictly routine and quiet life have been known to live for many decades with chronic cavitary disease of the lung or kidney or chronic sinuses draining through the skin—and without chemotherapy In such cases the sputum or other discharge is usually scanty although it continues to be bacilliferous One effect of chemotherapy although it falls short of bringing about the closed negative state of lesions is the reduction of exudate and discharge from persisting defects and this at least helps prevent the spread of infection into healthy parts Some patients seem to derive such benefit from chemotherapy for a number of years but the duration is limited by the emergence to predominance of drug resistant tubercle bacilli

Age of the patient is of interest prognostically although this is offset largely by the use of chemotherapy During adult life and old age men are at greater risk statistically than women and one may speculate that the difference is related partly to the poorer hygiene of living of the former Elderly men have more emphysema and other pulmonary damage from past neglected respiratory infections and occupational exposures such as that to siliceous dust and these help increase their vulnerability to progressive tuberculosis Some of these men are homeless recluses who show up for treatment only when their disease is far advanced their resistance depleted and their responsiveness to chemotherapy hopelessly feeble or nil

Treatment of Pulmonary Tuberculosis The need for treatment is usually self-evident when the patient has overt symptoms of active disease But in addition there is a large category of patients in whom the indications are not so clear-cut Most of these are brought to notice by routine roentgenographic examinations of the chest Since the patient with a small active lesion often presents the vaguest of symptoms or none at all the importance of determining its significance cannot be overemphasized The prompt and proper treatment of these cases yields results far superior to those achieved after more extensive invasion and destruction of tissue have occurred The problem therefore is to distinguish these cases from those in which apparently healed and inactive lesions are found It is simplified if certain data from previous examinations are available An authentic negative tuberculin test within the previous several years is reliable evidence that the newly developed pulmonary lesion is of recent origin presumably the result of a primary infection and therefore in need of treatment Likewise a roentgenogram taken several years previously and interpreted as normal has the same significance except that no inference can be drawn as to the time of infection Lacking such help the physician must rely on his current findings An adolescent or young adult patient presenting a lesion without definite evidence of fibrosis and calcification usually should have the benefit of treatment for at this age such lesions are almost always of recent origin and active furthermore this age carries with it a predisposition to rapidly progressive disease For the same reason young people with apparently fibrotic and calcified pulmonary lesions should be studied closely since these older foci usually harbor infection which sometimes becomes active at this time of life or later and may require treatment for its control

Older patients who appear healthy and whose lesions are judged to be densely fibrotic and calcified do not require treatment but only a roentgenographic examina

quence in numerous cases was chronic pleural infection sometimes with a bronchopleural fistula and an incarceration of the lung in an enveloping fibrous membrane which more or less interfered with re expansion at the termination of treatment Because of its advantages modern treatment with chemotherapy has almost completely displaced pneumothorax therapy

The *choice of chemotherapy* is determined chiefly by the known properties of the drugs (see p 257) Among the most generally employed regimens are isoniazid and PAS and streptomycin and PAS In very acute and severe cases it may be reasonable at the start of treatment to administer the three drugs concomitantly at least until the infection has come under good control Or it may be wise to administer for a time relatively large doses of isoniazid with the usual does of PAS or streptomycin Later it may be deemed better to reduce the dosage to the levels and intervals which help to avoid toxic effects and the early development of drug resistance Once the lesions have reached a point of stability and promising healing an effective regimen of chemotherapy should be continued arbitrarily for another year or more in the moderately or far advanced cases In the minimal" case approximately six months may be sufficient In the advanced bilateral cavitary case in which full recovery cannot be expected chemotherapy should be continued indefinitely and different regimens may follow one another as bacterial resistance devel ops to the first defense drugs In this way symptoms may be somewhat ameliorated and life prolonged

The hospital or the home may be a suitable place for treatment depending on the exigencies of the case It is significant that in many tuberculosis sanatoriums the number of patients treated today are no fewer than the number treated ten years ago but the average length of residence is materially shorter Most patients with overtly active disease profit by hospital treatment during the early weeks or months Toxic effects of poorly tolerated drugs become manifest usually within the first month or two of chemotherapy during this time close observation may be necessary to detect the early signs of harm and to make indicated changes in the regimen Also in the hospital it is usually more feasible to conduct the frequent examinations which in the early period measure the quality and degree of response to treatment If this is not satisfactory and surgery later is probably indicated proper preparation can be made for it Another reason for hospitalization may be the removal of the patient from the home until he is no longer likely to infect the other members of his family

After the control of the disease has been reliably achieved and the prospect of firm healing seems assured the patient may be sent back home to continue treatment there This presupposes of course that the conditions there are hygienic and reasonably conducive to his recovery and that the family is understanding and cooperative There are a good many patients who are homeless or customarily live alone and who need to receive most of their treatment in hospitals There are also patients with advanced chronic disease who unless they are affluent and otherwise exceptionally favored need some kind of permanent shelter perferably in a good institution where perhaps they may be given some light employment

Many recovering patients benefit from the intelligent assistance which they may receive from friends physicians and social agencies as they return to their social group regain their self confidence and resume some gainful occupation A necessity during treatment is the education of the patient on the nature of his disease and the modifications in his routine of living which it may impose immediately and in the future This is done best by the physician who has had considerable experience but it may be learned readily also by the inexperienced if he is seriously interested

Treatment of Special Symptoms *Cough and expectoration* if traceable usually to excavating lesions of the lungs and sometimes also to tuberculous laryngitis and bronchitis are best controlled by rest treatment and chemotherapy The patient is instructed to suppress coughing if possible and to expectorate by gentle clearing of the throat However it may be necessary to give sedatives such as codeine sulfate 0 03 gm at intervals of three or four hours or longer so that the patient may get sufficient rest sometimes this may be supplemented with a hypnotic at night For the distressing cough of patients who have considerable bronchitis steam inhalations perhaps with the addition of some medication like creosote or tincture of benzoin may be alleviative

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symptoms respond satisfactorily but in the mild and subacute forms this may occur within several weeks As treatment continues the maximal effect to be expected next is the disappearance of cough and expectoration and of other symptoms then the patient is usually gaining weight and feeling well During subsequent months the important criteria are the disappearance of tubercle bacilli from the sputum and gastric contents and evidences by physical and roentgenographic examination of progressive fibrosis with the closure of cavities Chemotherapy is continued throughout but there is no absolute criterion of the degree and duration of rest to be prescribed in these later months Some patients do well without a continuation of extra hours of bed rest beyond a good night s sleep perhaps with a short afternoon nap while others become easily fatigued these immediate sensations are significant A further important condition is that which best favors progressive and firm fibrosis of the lesions the surest safeguard against a relapse—early or after some years of inactive infection Unless compromises are forced by the urgency of returning to full time work or by other circumstances it is wise to give these recovering patients the benefit of the added insurance which is provided by a prescribed routine of rest and activity for six months or a year after the point of complete freedom from symptoms absence of tubercle bacilli from sputum and gastric contents and favorable anatomical healing and stability of lesions has been reached in some this activity may include light part time work

Throughout the course the standard guides are obtained by a systematic observation of the patient s symptoms a record of his temperature pulse and body weight and of the amount and character of the sputum Physical examination may reveal significant changes in the lungs particularly a diminution of rales but periodic roentgenograms are required to demonstrate the resolution of exudate the change in the size of cavities and the later delimitation by fibrosis Early the roentgenograms should be taken every week or two then after the stabilization of lesions at intervals of a month or more Counts of blood cells are made at the start but need not be repeated frequently unless there is an abnormality Estimations of the erythrocyte sedimentation rate and of the serum proteins may be of value especially during the subclinical healing phases of the disease An important necessity is the periodic microscopic examination and culturing of the sputum for tubercle bacilli and if it is negative the culturing of gastric contents Often a positive culture is the only demonstrable evidence of an unhealed lesion In such cases the cultural determination of the susceptibility of the bacilli to various drugs may be indicated

The foregoing information is related mainly to those patients with limited disease who under treatment go on steadily to improvement and eventual firm healing But there are many advanced and complicated cases in which the treatment mentioned does not accomplish these ends Usually because of the extent of destruction of tissue an impasse is reached where symptoms are more or less controlled but healing of the lesions does not occur to a comparable degree Large caseous residuals and cavitary defects persist which are a constant threat of later relapse If not too extensive these are best eliminated by *surgical resection* Segments of lobes entire lobes or the whole lung may be removed depending on the degree of involvement The operation involves the risk of complications including pleural infection and bronchopleural fistula but this is minimized by the proper choice of cases and timing of the surgery It is advisable to delay the operation until severe symptoms have subsided and the pulmonary lesions have been brought under good control but not until the tubercle bacilli have become resistant to available drugs If as a result of the resection a considerable unfilled pleural space remains it is often necessary at a subsequent operation to obliterate this by *thoracoplasty*—removing sections of a few or many ribs This operation is sometimes chosen in lieu of resection especially if the disease is too extensive to be removed but a chronic apical cavity may be expected to heal when its walls are allowed to collapse and come into contact Other measures to produce partial reduction of the volume of the lung include *paralysis of the hemidiaphragm* by crushing the phrenic nerve in the neck and *artificial pneumoperitoneum* but the value of these is usually questionable and limited *Artificial pneumothorax* was widely practiced usually to collapse one diseased lung for many years prior to the advent of chemotherapy The procedure continued in the given case by refills of air into the pleura for many months or several years had many excellent results but was attended by great risk of tuberculous pleural effusion empyema and fibrosis The conse

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Treatment of significant hemoptyses is designed to arrest the bleeding and to prevent a dissemnation of the infection in the lungs by aspiration of contaminated blood The patient should be in bed and in order to restore calm and quiet may be reassured justifiably that the bleeding will subside Violent coughing favors aspiration of the blood into healthy alveoli If the patient is unable sufficiently to restrain the impulse codeine sulfate 0 03 to 0 06 gm may be given hypodermically Morphine is seldom indicated and then only in small doses 0 008 to 0 01 gm Too much sedation depresses the reflexes unduly and may permit the retention of clots in the bronchi which is undesirable For a day or two after the initial hemoptysis dark clots may be expelled or fresh bleeding may occur usually in diminishing amount If the hemorrhages are large or frequently repeated especially in cases in which the disease is predominantly unilateral artificial pneumothorax may relax the lung and with it the bleeding vessel this procedure as a rule is effective Usually however pneumothorax is postponed for a few days or longer until accumulated blood has been cleared from the air passages since this lessens the possibility of acute pneumonic reactions and serofibrinous pleurisy after the pneumothorax If pneumothorax fails other forms of collapse therapy may be considered in emergencies occasionally thoracoplasty or resection of a cavity bearing lobe is indicated without delay However most hemoptyses subside after the loss of a small or moderate amount of blood and treatment may then be continued according to the usual indications During and for a few days after the hemoptysis the patient is given a soft or light diet according to his desires and it is not necessary usually to restrict this to fluids The patient is encouraged to lie on the affected side but during the waking hours he should change his position from time to time since this aids in expelling clots of blood Hemoptysis is relatively very infrequent while a patient is receiving chemotherapy if bleeding does occur new areas of pneumonic infiltration may follow but the continued therapy usually prevents much caseation and rapid resolution is often observed

Dyspnea of sudden onset usually is due to acute pneumothorax or pleurisy and is treated accordingly In advanced fibroid cases the symptom may become aggravated during attacks of acute bronchitis or bronchopneumonia when oxygen therapy is indicated for relief

Pain in the chest is traceable most often to pleuritic involvement strapping with adhesive plaster may give relief

Night sweats are relieved usually by rest in bed and proper nursing Drugs such as atropine or agaricin have little effect The patient should not be covered too heavily with bed clothes and the room should be airy and cool Alcohol rubs or baths before retiring are helpful After the sweat the clothing should be changed and the patient should be given an alcohol rub

Anemia is treated by a good general diet and by appropriate chemotherapy and vitamins as indicated Sometimes the most effective measure is the proper treatment of a complicating intestinal tuberculosis

Rehabilitation, which consists in developing plans for good living and suitable work after recovery may be instituted as soon as conditions warrant In many instances good morale and cooperation in treatment are promoted by encouraging the patient to see the goal of recovery ahead and by educating him to plan according to probable future opportunities and limitations Early in his treatment his aptitudes may be estimated by approved testing he may receive expert advice on vocations for which he is suited and when able begin study and training as he chooses In many hospitals and sanatoriums facilities and trained personnel are now available to render such services to patients

Maintaining Arrest and Avoiding Relapse In many advanced cases of tuberculosis the physician must recognize the impossibility of complete arrest of the disease and strive only to alleviate symptoms But when there is a prospect of returning the patient to useful life it is important to estimate when treatment has been sufficient to assure stability of the disease in the situations he is obliged to face later

According to the standards of the National Tuberculosis Association the disease is considered inactive when the lesions have remained apparently healed tubercle bacilli have not been demonstrable and the patient has been symptom free for at least six months As the lesions still harbor viable tubercle bacilli and relapse is possible the gains are to be maintained and consolidated during the next several years Experience shows that if the patient goes through two years with continuing "arrest the chance of relapse later is greatly minimized During this time close and systematic medical observation and advice are important as is the cooperation of the patient in following faithfully a prescribed

daily routine In most successfully treated cases six months to a year of "arrest should elapse before the patient returns to work During the interval as far as practicable his daily schedule of activity should be increased gradually until it approximates that which he expects to continue at work Patients who have followed light or sedentary occupations usually do best in returning to them particularly if the employer is willing to make some concessions pending complete rehabilitation One half day s work may be safe at first to be gradually increased during the following months or years Other patients often have to be educated for a new occupation since laborious work under unfavorable conditions is always to be interdicted

Periodic medical supervision is indicated indefinitely after recovery At first the patient should be seen once a month during this time he should be questioned about symptoms the sputum should be searched for tubercle bacilli and a roentgenogram should be made for comparison with those previously accumulated Continued good general health absence of tubercle bacilli and unchanging roentgenographic shadows (except perhaps for slight further contraction of the fibrotic lesions) permit as a rule continuation or expansion of the daily routine After three or four months the interval between examinations may be gradually lengthened but for the first two or three years the patient should be observed in this way every three to six months and afterward at least once a year The appearance of symptoms should always be the occasion for medical examination to determine the cause

TUBERCULOSIS IN CHILDREN

In children the lesions of primary pulmonary infection have features which differ somewhat from the manifestations in adults The primary parenchymal lesion is less likely in children to go on immediately to progressive excavation but there is a pronounced tendency to gross involvement of the bronchopulmonary tracheobronchial and other mediastinal lymph nodes Consequently physical examination though it should not be omitted does not reveal the true nature of the lesion as well as it usually does in adults Roentgenographic examination is a necessity In children more than in adults enlarged lymph nodes may compress the bronchi in the root of the lung which in turn may lead to nonspecific changes distally in the parenchyma Extension of the infection from the nodes may involve adjacent structures eventually resulting in damage such as ulceration and stenosis of the bronchus and traction diverticula of the esophagus On the other hand inflammation of the nodes often subsides and their size diminishes strikingly leaving relatively small calcific residues (Fig 31)

Because of the frequent hemic dissemination of tubercle bacilli there is a relatively high incidence of meningitis and generalized miliary disease among infants This according to Wallgren is most apt to occur within the first three months after the primary infection Barring such catastrophes lesions may evolve within a few months or even after a period of years at local sites such as the bones and joints and the genitourinary tract Also although fatalities are relatively rare between the ages of two and ten or twelve latent pulmonary lesions remaining from the primary infection acquired in childhood have a definite tendency to flare up in adolescence and early adult life This hazard increases somewhat in proportion to the greater extent and caseous character of the latent lesions

Treatment The local primary lesions in the parenchyma and lymph nodes of children tend to run a benign course and to undergo considerable resolution On this



Fig 31 Apparently calcified tuberculous lesions in the right lung and bronchopulmonary lymph nodes (primary complex)

account it is difficult at times to estimate in individuals the additional benefit derived from chemotherapy Experience with large groups of children however has yielded evidence of the powerfully favorable effects of the drugs A number of clinicians *among whom Edith M Lincoln* and her associates at Bellevue Hospital have had a long and well documented experience have reported a lowering of the fatality of manifestly active disease by approximately 90 per cent As in adults widely *destructive cavitary disease of the lung* may be brought under sufficient control to permit surgical resection Bronchial (endobronchial) tuberculosis due to direct extension from contiguous caseous lymph nodes a relatively common problem in children *is not strikingly influenced by chemotherapy* (Lincoln *et al* 1956) probably because of the persistence of infection in the underlying focus By contrast in adults in whom bronchial lesions are usually more superficially situated in the mucosa and caused by *infection from draining parenchymal cavities* the response to such treatment is generally very good A regimen which contains isoniazid has been shown to reduce the risk of meningitis in infected children and this is strong evidence that such chemotherapy *suppresses the infection* in local lesions and also arrests the destruction of tissue which in some cases causes a break in the pulmonary vein and allows the escape of bacilli into the blood stream

It has become a common practice to treat infected children under two years of age with chemotherapy chiefly to avoid these early complications (Bentley 1956) and some advocate this up to the age of four It remains to be seen however whether such practice will reduce the risk of a flare up of latent lesions in adolescence

TUBERCULOSIS OF THE LARYNX TRACHEA AND BRONCHI

Tuberculous laryngitis is one of the common complications of chronic pulmonary tuberculosis The lesions may be chronic and localized or acute exudative and diffuse The lesion usually appears first at the level of the vocal cords or the arytenoids in the posterior part of the larynx There may be a diffuse swelling or tubercle formation of the mucosa in the interarytenoid space a the *posterior* end of one or both vocal cords or in the region of one or both arytenoid cartilages The inflammation may become almost completely resolved or it may progress with caseation and ulceration The irregular ragged shallow ulcers are found usually in the locations mentioned Later granulations may develop which have a serrated granular or tubercular form If extensive fibrosis may cause slight stenosis of the larynx The early symptoms are huskiness and hoarseness of the voice dryness and slight soreness of the larynx This may be noticed only on awaking or after talking but usually continues beyond the time expected for simple catarrhal laryngitis Laryngoscopic examination then may show the typical changes Later if the lesions progress hoarseness becomes chronic and continuous and the dryness and irritation may cause moderate or severe coughing Pain is not usually a pronounced symptom unless deep invasion of the laryngeal cartilages occurs One of these the epi*glottis may become greatly enlarged swol*len red and finally deeply ulcerated Such extensive disease results in dysphonia severe dysphagia and salivation and the patient s nutrition may be seriously impaired In treatment an important principle *is vocal rest the patient being instructed* to abstain from using the vocal cords In these cases specific chemotherapy is indicated not only for the laryngeal disease but also for the pulmonary tuberculosis the regimens being the same The response of *the laryngitis* is usually very satisfactory sometimes dramatically so Painful symptoms often disappear rapidly

The *bronchi* leading from a tuberculous pulmonary cavity usually are invaded and in some cases lesions in the *larger bronchi* or *trachea* assume important clinical significance Shallow lenticular ulcers of the mucosa are not uncommon and more pronounced lesions develop occasionally in patients especially women with *longstand*ing pulmonary disease The bronchial wall may be attacked also by lesions in contiguous lymph nodes The bronchial lesions consist of ulcers which are superficial or penetrate to or through the cartilage or of granulomatous and fibrous formations which may partially occlude the lumen Healing in the early stages leaves little or no scar but more *advanced lesions may* be followed by extensive organization of the bronchial and peribronchial tissues with contraction and cicatricial stenosis The affected bronchus may fail in its function as a drainage tube and in this event the related segment of the lung becomes involved with secondary pyogenic infection resulting in bronchopneumonia which may be necrotizing and associated with bronchiectasis The diagnosis depends on eliciting the history of symptoms such as persistent

severe coughing and wheezing and the auscultation of rhonchi confined mostly to one side of the chest or to one lobe Foulness of the sputum is suggestive of complicating anaerobic infection which often involves the parenchyma distal to the bronchial obstruction Roentgenographic evidence of obstructive emphysema or cavities which appear distended and partly filled with fluid or of diffuse pneumonia is suggestive Bronchoscopy may disclose the lesions Chemotherapy for the pulmonary tuberculosis is often quite effective in part because of the reduction of purulent discharge passing over the bronchial surfaces At the same time the subsidence of bronchial edema allows better drainage of pulmonary cavities thus favoring their healing However if the bronchus becomes narrowly constricted during its fibrous repair lobectomy or even pneumonectomy may be necessary to prevent or remove the chronic destructive secondarily infected parenchymal disease which ensues almost inevitably

TUBERCULOSIS OF THE ALIMENTARY TRACT

Tuberculosis of the mouth appears most often as ulceration of the tongue which becomes infected as a rule by extension from a laryngeal lesion or through an abrasion caused by biting or other trauma from the teeth The lesion is situated most often on the margin but may involve the dorsum especially at the base The ulcer at first is superficial but progressive infiltration and caseation often follow with extensive destruction of the muscle The chronic ulcers are often fissured and yellow caseous or red granulating tubercles may be found in their depths The indurated base is usually palpable The ulcer is usually single but others may appear The diagnosis depends on the finding of such a lesion in a tuberculous patient and may be confirmed by demonstrating the organisms in curettings from the ulcer Biopsy is to be avoided unless necessary Specific chemotherapy may bring about partial or complete healing

Tuberculosis of the lip or gingiva is found usually under similar circumstances the lesion appearing much the same as that of the tongue An ulcer at the corner of the mouth may be fissure like and penetrate deeply

Tuberculosis of the salivary glands is rare possibly because of the alkaline reaction of the tissue (Vivoli *et al*)

Tuberculosis of the pharynx is found most often in association with lesions of the *tonsil* Infection of the latter may be due to surface contamination or to hemic dissemination from a distant focus Upon examining 2000 pairs of tonsils removed surgically Long Seibert and Gonzales found that the incidence of tuberculous lesions depends roughly on the prevalence of tuberculosis in the community it was 6 5 per cent in specimens from American Indians 2 5 and 0 25 per cent in those from Puerto Ricans and Philadelphians respectively The lesions are usually deep and focal In cases recognized clinically the tonsil is slightly or moderately enlarged and may show yellow or whitish caseous areas beneath the shiny mucosa later these break down leaving grayish yellow ragged ulcers One or both tonsils may be involved When the pharynx becomes infected secondarily the fauces soft palate and uvula become thickly seeded with granular miliary tubercles some of which have a minute yellowish center These coalesce break down and form fissured ulcers and the tissues may be slowly destroyed The pain is severe salivation profuse and dysphagia marked Such extensive disease is usually fatal unless it can be controlled early by specific treatment

Tuberculosis of the esophagus is relatively rare The upper end may be involved by direct extension from severe tuberculosis of the larynx Tuberculous lymph nodes of the mediastinum after caseation may perforate the esophagus discharging their contents or the perinodal inflammation may involve the esophagus without perforation In either event the cicatricial contraction may produce diverticula of the esophagus

Tuberculosis of the stomach is reported in a few cases of pulmonary disease at autopsy (up to 2 per cent) The lesions usually extend to the stomach from a contiguous adherent lymph node but they may result from surface contamination of the mucosa by swallowed discharges from the lungs The gastric wall may be infiltrated or there may be an ulcer usually near the pylorus which grossly resembles carcinoma

The *intestine* is most frequently involved the commonest site being the lower ileum and cecum The mechanism of infection is principally surface contamination with swallowed tubercle bacilli in patients with pulmonary tuberculosis (up to 70 per cent at autopsy) Much less often infection may be caused by primary invasion (*e g* contaminated milk) hemic dissemination or extension from tuberculous peri

tonitis Infiltration of the intestinal mucosa and lymphoid tissue usually is followed soon by superficial ulceration the ulcers may extend rapidly or become localized and chronic with an organizing granulating base and overlying fibrinous or fibrous peritonitis Sometimes as in the cecum the proliferative granulomatous changes become protracted leading to great thickening of the wall fibrous peritonitis and narrowing of the intestinal lumen the whole forming a tumorous mass Acutely progressive ulceration may involve several feet of the intestinal mucosa enclosing small islands of intact tissue Perforation of the wall by the ulcer is infrequent Small ulcers may heal and the mucosa apparently regenerate

The initial symptoms are indefinite and considerable ulceration may be found in patients who have never had abdominal complaints At first there is slight to moderate loss of weight vague indigestion loss of appetite irritability and secondary anemia Local symptoms may appear early or late as a change in the usual rhythm of the stools A short attack of mild diarrhea may be followed by constipation and after an apparently normal interval this may recur After many weeks or months diarrhea may become frequent and finally the patient will have ten to twelve evacuations during the day and night the diarrhea being watery and foul seldom bloody The diarrheal attacks are associated often with colicky pains in the lower half of the abdomen aggravated perhaps by taking certain foods such as raw fruit The patient may become emaciated Physical examination usually reveals no palpable masses and frequently no tenderness although the patient may complain of a little soreness on deep palpation especially in the right lower quadrant In certain mild chronic cases the recurrent pain simulates simple chronic appendicitis in fact the appendix may be involved in the tuberculous process Sometimes this is not suspected until the lesions are discovered on routine histological examination of the resected appendix In cases of tuberculous enterocolitis roentgenographic examination after a barium meal or enema may reveal spasticity filling defects and hypermotility of the lower ileum cecum and ascending colon Treatment consists first in proper general management and prescribed rest since these patients almost always have chronic pulmonary tuberculosis The diet should be bland raw fruits fruit juices and fat may have to be reduced or eliminated temporarily and vitamins given parenterally Medication to relieve pain and lessen the intestinal spasm may be indicated in the form of powdered opium or paregoric bismuth subnitrate or bismuth subgallate by mouth or calcium gluconate intravenously Specific chemotherapy is highly effective

Tuberculous ischiorectal abscess or *perianal abscess* and fistula are due usually to infection in a similar way and start with a localized painful perianal swelling which becomes acutely tender within a few days or several weeks If not incised this may perforate the skin to the exterior less often the wall of the rectum with the discharge of nonodorous pus in which tubercle bacilli may be demonstrated The resulting fistula is apt to be chronic and later to require surgical treatment However if the original abscess was rather superficial and drains freely it may heal satisfactorily with chemotherapy administered in the usual way Local applications of one or more of the drugs have been tried but this seldom seems to be necessary except following surgical resection of the fistula

GENERALIZED FORMS OF TUBERCULOSIS

Acute Generalized Miliary Tuberculosis

The disease occurs most frequently in young children or infants and occasionally in adult life especially in men over sixty years of age The patient may have been in perfectly good health previously or may have had some clinical or other demonstrable evidence of tuberculosis such as roentgenographic signs of mediastinal lymph node involvement (Fig 31) The onset may be abrupt with chilliness prostration aching in the muscles headache and drowsiness or gradual with malaise weakness and fatigue for a period of a few days or a week before the patient becomes prostrated The temperature may rise at once to 103° or 104° F in the afternoons or attain this level gradually during a week or so Night sweats may be profuse the soft tissues waste rapidly and the patient is overcome by weakness Localizing symptoms depend on the predominant distribution of miliary tubercles Dyspnea and cyanosis may become pronounced because of the extensive and rapid invasion of the lungs but there is usually no cough or only a slight hacking In other cases peritoneal symptoms such as pain distention and constipation may predominate Effusions may accumulate in the serous cavities with the well known clinical manifestations of their presence if they are profuse

Physical examination initially shows only the general effects of the toxicity After a week or more fleeting rales may be heard in the lungs later numerous and persisting fluid may be demonstrated occasionally in the pleura or peritoneum less often in the pericardium The spleen becomes palpable *in only a minority of the cases* Tubercles are seen somewhat less frequently in the choroid of adults than of children The roentgenogram of the chest is *indeterminate* at first but usually shows characteristic stippling of the pulmonary fields within several weeks The leukocyte count usually remains within normal limits but occasionally becomes moderately elevated seldom above 20 000 per cu mm *Leukemoid reactions and aplastic anemia* due presumably to invasion of the bone *marrow are rare complications*

A biopsy of the bone marrow may show tuberculous changes and sometimes tubercle bacilli may be grown in cultures seeded with the aspirated marrow Occasionally the organisms are also grown from the blood but they seem to disappear soon after dissemination from the focus of origin ceases The situation may be aggravated by supervening meningitis which may develop early or late in the course In Debre s 170 cases of miliary disease in children meningitis occurred in 88 per cent of the acute forms and in about 50 per cent of the subacute

Treatment with combinations of specific drugs should be started as soon as the diagnosis is made Initially streptomycin (2 0 gm daily) and isoniazid (400 to 600 mg daily) are administered to adult patients Many prefer to add para aminosalicylic acid (10 to 15 gm daily) In early cases a *symptomatic* response with gradual lowering of the temperature to normal levels within two to eight weeks is the rule at the same time a gradual fading of the miliary shadows from the roentgenogram of the lungs is observed As the temperature becomes normal the dose of streptomycin is reduced to 1 0 gm daily and that of isoniazid to 200 to 300 mg daily chiefly *to avoid the toxic effects of the drugs* this regimen is continued for two or three months longer after which streptomycin is *further reduced to 1 0* gm three times a week (every other day) This regimen then is maintained for a year or more depending on the original severity of the case

The importance of isoniazid in the regimen of therapy is demonstrated by the experience of the Veterans Administration Army and Navy hospitals reported by J H Williams Jr (1957) Compared with a five year survival rate of 52 per cent after treatment with streptomycin alone 57 per cent with streptomycin sulfone and 80 per cent with streptomycin PAS the introduction of an isoniazid streptomycin regimen in 87 cases is credited with a two-year survival rate of 95 per cent None of these developed meningitis during a year or more of observation *after the start of treatment* whereas the incidence of this complication among 100 patients treated with streptomycin alone was 40 per cent and among those treated with streptomycin PAS it was 22 per cent

Subacute Forms

The subacute forms are likewise observed most often in the early ages but occasionally *also in adults particularly Negroes* Tubercle bacilli enter the lymph or blood stream perhaps at recurring intervals from a caseous focus The number of lesions established in various organs is only moderate and since the patient does not die soon time is sufficient to permit further local development with necrosis or partial healing Many bacilli are picked up by the lymphatics and come to rest in various regional lymph nodes The lungs are frequently involved the lesions being particularly prominent in the upper parts The *spleen kidneys liver and serous membranes* often participate

The variety of clinical *manifestations* is great but some are fairly constant The patient may have obscure fever which has persisted for days or weeks without other obvious symptoms except loss of weight malaise and fatigue In time peripheral lymphadenopathies may become apparent as in the auricular cervical axillary epitrochlear and inguinal regions A roent*genogram of the chest* may show only widening of the upper mediastinum from the lymphatic lesions The spleen may become palpable within a few weeks or months Other patients with similar fever reveal evidence only of an effusion in the pleura peritoneum or perhaps in several or all of the serous cavities Still others may be found to have genitourinary tuberculosis and *occasionally papulonecrotic* lesions of the skin give the first clue to the identity of the fever Multiple lesions *in the* bones and joints and in the eye may be associated some may become ulcerous or fistulous

The natural course unless interrupted by chemotherapy is *almost* always progressively unfavorable most patients die in

three to six months some with an acute miliary dissemination at the end A few survive longer when the disease may evolve in one or more local sites usually the lungs progressive cavitary lesions then may appear

Treatment is the same as that for the acute form Since the early course of the subacute forms is relatively mild and the diagnosis often uncertain necrosis in many of the disseminated lesions may have occurred before treatment is started Consequently the possibility of a late relapse may be greater than it is in the promptly treated acute case

Latent and Chronic Forms

It is not uncommon at autopsy to find tubercles originating obviously in hemic dissemination of the infection perhaps many years before distributed in such structures as the spleen liver kidneys lungs and lymph nodes These may be small even microscopic gray tubercles isolated in fibrous capsules Others are represented by encapsulated round calcified nodules Although these foci may still harbor living organisms and lead to local exacerbations they usually remain latent during the life of the person in whom they may be demonstrated by roentgenographic examination Lesions of disseminated fungal infections especially histoplasmosis often have a similar form and distribution and are to be strongly suspected in endemic areas Undoubtedly in the past many of these cases were wrongly interpreted as tuberculosis It may require the demonstration of the causative organism in the stained tissue to make the distinction

Among patients who recover from acute or subacute generalized tuberculosis it is to be expected that some may have local recurrences at sites where the lesions may not have healed sufficiently The lungs then may be the site of numerous scattered fibroid lesions which cause some functional difficulty and among them may be some small caseous lesions which progress break down and become the sources of bronchial dissemination It has become apparent however that scattered pulmonary lesions of a chronic nature are almost always the result not of blood borne infection but of bronchial dissemination from a sloughing local focus Spain has produced pathological evidence that tubercle bacilli in the blood stream are not completely filtered out in the lungs when pulmonary lesions of this origin were identified he always found lesions elsewhere chiefly in the abdominal organs (see Pathogenesis p 250)

Tuberculosis of the Serous Membranes

Any of the serous membranes may become infected usually singly but sometimes *in combination The pleura is most* commonly involved secondly the peritoneum less often the pericardium The way of infection is by direct extension from some contiguous tuberculous lesion less often by the blood or lymph streams The lesions appear as isolated tubercles or as fibrinous or serofibrinous inflammations Fibrinous changes usually are rather limited while serofibrinous inflammations involve the whole membrane which is edematous and red The serous exudate may be absorbed and fibrinous deposits may become partially or completely resolved As a rule however some of the endothelial lining is destroyed granulations develop and eventually are transformed into fibrous tissue adjacent surfaces may be bound together by firm adhesions in which lymph and blood vessels may develop In relatively few cases the effusion becomes purulent deep inflammation and granulomatous thickening of the serosa occur and this may undergo caseous degeneration Subsequent organization and fibrosis leave behind permanent thickening and adhesions of the membranes with distortions and retractions of adjacent structures The serous or purulent exudate may become loculated After some years if this is absorbed incompletely or slowly free cholesterol accumulates in the fluid and the organizing walls of the pockets become infiltrated with calcium salts Calcification of the pleura is seen occasionally calcifications of the pericardium less often calcification of the peritoneum rarely

Treatment of tuberculosis of the serous membranes should take into consideration that the infection is not primary here but originates most often in a local underlying focus Infrequently as a manifestation of hemic dissemination from a distant lesion it is treated as a part of the generalized disease Usually however attention is given to searching for the contiguous focus if this is not already manifest common sites are mentioned below The serositis may soon subside spontaneously or under treatment but this should be given until the underlying infection which obviously was active is assumed to be controlled Even though streptomycin isoniazid or

PAS administered in the usual way diffuses into serous and purulent effusions their absorption is apparently not hastened Given within a few days of the onset of the effusion the acute general symptoms may be ameliorated and the accumulation of fluid may be limited

TUBERCULOSIS OF THE PLEURA

The commonest form is fibrinous pleurisy and this usually overlies a pulmonary lesion Serofibrinous pleurisy develops in approximately 5 per cent of all cases of pulmonary tuberculosis it may also be a manifestation of generalized tuberculosis It is discussed in detail in the Section on Diseases of the Pleura By the addition of adequate chemotherapy to the treatment of patients with tuberculous pleural effusion but without visible parenchymal disease Emerson (1957) found the five year morbidity rate reduced to 4 per cent among 83 patients This occurred in spite of the fact that there was no reduction in the duration of the effusion the accelerated erythrocyte sedimentation rate or the duration of the pyrexia

Tuberculous empyema is related usually to some peculiar situation such as pleural ulceration and rupture or artificial pneumothorax and is considerd in this connection The effusions complicating pneumothorax treatment are usually serous or serofibrinous but in some cases there is a large output of polymorphonuclear leukocytes which rapidly undergo degeneration giving the fluid at first a cloudy appearance and later a thick light yellow or greenish creamy consistency Tubercle bacilli may be demonstrable easily microscopically and may appear in large clumps A thick coating of fibrin and coagulated nucleoprotein is deposited on all the pleural surfaces Unless the exudate is absorbed early organizing pleurisy enveloping the collapsed lung may bind this down and prevent its re-expansion

Pneumothorax in tuberculous cases is related either to the ulceration of a subpleural caseous focus or to the rupture of a subpleural bulla which has developed secondary to the fibrosis For a detailed discussion of this entity the reader is referred to the section on Diseases of the Pleura

Tuberculosis of the peritoneum may be the result of hemic infection or of extension from local lesions such as retroperitoneal lymph node involvement or salpingitis Fibrinous inflammation in the visceral peritoneum at the site of intestinal ulcers is a common finding General involvement may be miliary serofibrinous or plastic and adhesive Serofibrinous peritonitis may have an acute or insidious onset with constitutional symptoms like those described for serofibrinous pleurisy Abdominal pain and tenderness are usually slight or moderate occasionally very intense Initially there may be some vomiting and diarrhea but later constipation is the rule Abdominal distention may be great due to ascites and tympanites but in other cases the wall is spastic and scaphoid As adhesions develop the exudate may become loculated in pockets and the omentum and intestine matted

Exudative peritonitis is most common in children and young adults but may occur even in old people it is observed more often in Negroes than in white persons and in females than in males Occasionally it is a complication of cirrhosis of the liver Under treatment which includes chemotherapy for a vear to two years the prognosis for recovery is good (It is also to be assumed that the treatment of generalized tuberculosis will abort or prevent peritonitis in many cases) Mechanical symptoms may require evacuation of the fluid to avoid perforating the gut this is done best by a small surgical incision Laparotomy is unnecessary in most cases In female patients tuberculosis of the fallopian tube may prolong the peritonitis and favor chronicity in such cases salpingectomy may later be indicated

Plastic adhesive peritonitis usually is a later development of fibrinous or serofibrinous inflammation Fibrous contraction may produce narrowing of the lumen of the bowel the coils of which may be bound together in large inseparable tangles Between the hyperplastic and caseous lesions tuberculous exudate sometimes purulent may be pocketed Abdominal examination mav reveal irregular masses of involved omentum matted intestine caseous deposits or enlarged lymph nodes These may be numerous or confined to a single section such as the right lower quadrant surrounding the cecum Aside from the manifestations of chronic toxicity local symptoms may become distressing on account of the fixation and stenosis of the bowel There may be constipation obstipation or occasionally obstruction Rarely the intestine is perforated and tuberculous pus mav drain from the peritoneum into it

Treatment is general and symptomatic unless the disease is localized and accessible such as a hyperplastic process in and surrounding the cecum this may be re

sected surgically Postoperative abdominal fistulas which may be fecal are not uncommon In most cases especially those treated early the course of the disease is arrested or favorably influenced by chemotherapy Kahrs reports the outcome of 169 cases treated in Norway between 1930 and 1948 (mostly without chemotherapy) He found the serous type to have the most favorable outlook (20 deaths in 73 cases after 2 5 to 20 5 years) while the fibrinopurulent and purulent types (9 cases) all ended fatally

Tuberculosis of the pericardium may represent an extension from the pleura in which case the lesions are usually of a localized fibrinous hyperplastic or adhesive character giving rise to few or no symptoms Serofibrinous pericarditis is caused by direct extension of the infection from adjacent caseous lymph nodes or less often by hemic infection Among all cases of pericarditis tuberculosis is identified as the cause in approximately 7 to 11 per cent (Reeves Griffith and Wallace) Aside from the manifestations of toxicity symptoms and signs referable to tamponade of the heart may be found the embarrassment may be relieved by paracentesis The effusion may continue reaccumulating and after three to six weeks loculation may occur because of the formation of fibrinous adhesions Caseation is observed occasionally especially in Negroes and may extend *into the myocardium In the few cases of* recovery the layers of the pericardium may adhere completely and in time the shrinkage may lead to chronic constrictive pericarditis with functional impairment In this disabling situation the operation of pericardiectomy or cardiolysis may effect partial or complete relief in 60 per cent of the cases (Heuer and Stewart)

Treatment is basically the same as that for tuberculous pleurisy and should take into consideration associated disease in the lungs and elsewhere Chemotherapy is indicated and usually should be continued for a year or more

TUBERCULOSIS OF THE LYMPH NODES

Lymph nodes may be infected by tubercle bacilli entering the lymphatic stream from a lesion in the tributary region or arriving by way of the blood stream Most often the lesions are limited to a single chain frequently the mediastinal system However in generalized forms of tuberculosis multiple scattered lymphadenopathies are demonstrated commonly in the superficial and deep chains The lesions may appear as acute subacute or insidious inflammatory swelling of the nodes with gradual caseation and necrosis Perinodal inflammation and agglutination with adjacent nodes may follow later liquefaction rupture and sloughing of the contents through the overlying tissues particularly in superficial involvement As the inflammation subsides calcification of the caseous residues may develop slowly during a period of years and the lesions may remain as permanently enlarged firm usually discrete nodes Sometimes chronic fistulas usually superficial persist and may burrow widely causing extensive degeneration of the skin and subcutaneous tissues (scrofuloderma) Most often lymphadenitis is of a mild hyperplastic type with only a minimum of caseation The lesions may be chronic or may subside and become reactivated repeatedly after long or short intervals of time without any evidence of liquefaction or sloughing In the chronic systemic forms of tuberculosis the lymphatic system may harbor most of the lesions and account for the protracted ill health including exacerbations of low fever from time to time

Specific chemotherapy for tuberculosis of lymph nodes is subject to the same general principles previously discussed and to an estimation of the prognosis Often the disease is a mild self limited process and the important thing is to build up general re*sistance to avoid a recurrence* In acute cases specific therapy may help materially to halt the inflammation and promote resolution but a lasting effect on the caseous components is not to be expected These require a long time for natural healing may liquefy in spite of specific therapy and when accessible may eventually require surgical treatment

Mediastinal and bronchopulmonary lymph node tuberculosis is observed most often in young children following the primary infection Constitutional symptoms may be mild or entirely lacking Massive lesions may produce pressure giving a variety of symptoms such as stridulous cough simulating whooping cough constant or intermittent wheezing respiration sometimes simulating asthma less commonly stridor dyspnea and cyanosis Localized pressures on the bronchi may irritate and compress the tube resulting in collapse of the lobe or the lung or the development of nonspecific necrotizing bronchopneumonia and possibly bronchiectasis Perforation of the nodes through the trachea more often the bronchi occurs most often during infancy

and early childhood and very seldom during adult life the tubercle bacilli thus discharged may then be aspirated into the lung causing tuberculous bronchopneumonia Calcified nodes similarly may ulcerate through the bronchi (broncholithiasis) Physical examination usually is not helpful unless the mass is very large then it may be suspected by dullness and altered breath and voice sounds extending beyond the spine or sternum on one or both sides The roentgenogram reveals the lesions unless they are small and concealed by other structures the shadows include bulbous enlargements of the hilum widening of the mediastinal density and the round and oblong homogenous or granular opacities of calcification With few exceptions the tuberculin test is positive and often there are typical lesions also in the lungs or elsewhere Occasionally physical signs and symptoms of bronchial stenosis or tracheal and venous obturation may be elicited Diseased nodes which are not greatly enlarged or extensively caseated have a tendency to subside and heal without special treatment and the finding of calcified residues in later years is the common evidence of this The need for and duration of chemotherapy and supportive treatment are based therefore on the recognition of certain risks which are somewhat peculiar to primary tuberculosis These include recently acquired active and extensive lesions disease in the parenchyma of the lungs or elsewhere and the age of the patient In infants for instance chemotherapy is intended to avoid the development of systemic disease as well as to promote the healing of the primary sources Surgical removal of massive diseased nodes has been accomplished but is seldom undertaken

Cervical lymphadenitis is a common form but in the United States has become much less prevalent since the early nineteen hundreds The disease which was known in earlier times as scrofula or king s evil has been reduced through the elimination of tubercle bacilli from milk and the prevention of infection in childhood The lesions may be confined to one or several nodes or may encircle the neck anteriorly from ear to ear The upper deep cervical nodes are most frequently affected as a rule the lesions are more pronounced on one side Infrequently the acute swelling is so marked as to impede the motion of the neck and to displace the treachea If the onset is insidious the lumps may be discovered purely accidentally Tenderness is slight or moderate unless the overlying tissues become involved The skin usually appears healthy but may become red tender and gradually thinned out until perforation occurs A thick or nummular purulent discharge follows and drainage may continue for a long time Neglect of the condition may result in fistulas in various parts of the neck and in the upper thorax Treatment during the acute stages includes the use of chemotherapy This usually controls the active inflammation and dries discharging sinuses Afterwards surgical excision of chronically enlarged and necrotic nodes may be indicated if these are deemed likely to break down again Chemotherapy then is continued until healing is well established In cases of fluctuant nodes and draining sinuses treatment by wide incision irrigation and packing with streptococcal enzyme (streptokinase streptodornase) has been reported by Anastasiades *et al* (1957) to produce satisfactory results in a majority of twenty nine children

Abdominal lymphadenitis may be part of a generalized infection or may result from lesions in the intestine peritoneum or other adjacent organs Usually there are no specifically localizing symptoms but when the involvement is moderate or extensive vague abdominal pain constipation and indigestion may be complaints Sometimes the condition simulates chronic appendicitis Advanced wasting disease in infants and young children is known as *tabes mesenterica* Unless the lesions originally were extensive or part of generalized tuberculosis the tendency to heal is striking In chronic cases the infection may spread through adherent lymph nodes into the stomach duodenum pancreas or liver Adjacent iliac veins may become thrombosed rarely a node perforates and discharges into the aorta

TUBERCULOSIS OF THE URINARY TRACT

The kidney is the most frequent site of tuberculosis of the urinary tract the infection usually being blood borne In males the infection sometimes extends to the urinary tract from the genitals The disease is much more prevalent in adults than in children and is observed two to four times as frequently in males as in females The finding of microscopic tubercles in the kidneys is common at autopsy but gross lesions are detected in 10 per cent or less of all cases of chronic pulmonary tuberculosis The disease often occurs in patients who have never suffered from pulmonary lesions the presumption being that the infection was carried from a primary focus which subse

quently healed Renal lesions may be latent for a long time before causing clinical symptoms The early lesion is usually in or near the glomerulus and bacilli may pass from this through the tubules to the papilla Caseation and ulceration may be limited or extensive resulting in the formation of small fistulas and the discharge of bacilli into the renal pelvis and ureter These more resistant structures also may be invaded Often the kidney becomes more or less excavated Occasionally the caseous lesions may be encapsulated or the ureters become sealed off then calcareous changes may develop The bladder may be infected with bacilli carried in the urine tubercles and ulcers about the ureteral orifice appear and if the invasion is wide later fibrous shrinkage may reduce the capacity greatly It is to be assumed on pathological evidence that the renal lesions are bilateral but progressive destructive disease may be confined to one kidney

The symptoms include polyuria hematuria pyuria dysuria and strangury but at the inception renal tuberculosis usually is symptomless Similarly physical examination at the start may be entirely negative Later slight tenderness may be elicited on palpation of the kidney or in the upper lumbar region posteriorly Constitutional symptoms if any usually are slight The condition is to be suspected particularly in a patient with pulmonary tuberculosis in the presence of unexplained albuminuria hematuria or pyuria especially the last two even if the quantity of blood or pus is small Dysuria or cystitis not explained otherwise should always be investigated Examination of the urine may show small or moderate amounts of albumin an abnormal number of erythrocytes and pus cells Intensive search usually reveals the presence of tubercle bacilli (see Demonstrating Tubercle Bacilli p 253) Pyelography cystoscopy and ureteral catheterization are used to demonstrate the extent and location of the lesions

Specific chemotherapy generally accepted as the first treatment of renal tuberculosis is usually continued for two years or more Various drugs have been given concomitantly with good early results but a lengthy follow up of patients (J H Williams Jr Lattimer 1956 1957) indicates that the best regimens are those which include isoniazid and PAS possibly with the addition of streptomycin Among the cases treated early healing has been satisfactory remaining so after approximately five years In the more advanced cases with marked destruction of tissue the relapse rate is apparently greater than 10 per cent and nephrectomy may be indicated The response to chemotherapy is judged by the rate of disappearance of abnormal elements from the urine It is particularly important by repeated cultures of the urine to note the time of disappearance of tubercle bacilli and their possible later reappearance

TUBERCULOSIS OF THE GENITAL TRACT

Genital tuberculosis was found in 1?7 per cent of 1143 autopsies on tuberculous subjects by Auerbach at the Seaview Hospital—14 4 per cent of the males autopsied and 10 4 per cent of the females It is almost always caused by blood borne infection from lesions elsewhere in the body In 41 cases in females Auerbach found the fallopian tubes involved in 97 5 per cent the uterus in 58 5 per cent and the ovaries in 31 7 per cent The cervix is seldom affected the vagina and labia rarely The most common sequel of salpingitis is localized or diffuse peritonitis Both tubes may be involved but the lesions are usually unilateral There may be few or no localizing symptoms if any they appear as dull vague pains in the lower abdomen accentuated perhaps during menstruation The menses may be scanty irreguar or absent There may be slight or moderate leukorrhea tubercle bacilli may be found in the discharge or in the menstrual blood Curettage may bring away endometrial tissue revealing tuberculous changes in microscopic examination Pelvic and sometimes abdominal examination may reveal an elongated round mass a few centimeters in diameter in the pelvis The lesions may heal spontaneously if they are not extensive but if they are chronic surgical resection after a prolonged course of chemotherapy is favored sometimes to eliminate the focus and prevent extension to the peritoneum Exacerbations of the disease especially if the uterus is involved may be caused by pregnancy prolonged postpartum bleeding not otherwise explained should arouse the suspicion of tuberculosis Chronic or healed tuberculous salpingitis may cause sterility

Male genital tuberculosis usually is manifested first in the epididymis but pathological examinations suggest that the initial focus usually is in the prostate the epididymal lesion being a secondary extension In 105 cases examined at autopsy Auerbach found the prostate involved in 95 2 per cent the seminal vesicles in 61 9 per cent the epididymis in 48 5 per cent

and the testes in 29 5 per cent Ljunggren found associated involvement of the kidneys in 50 per cent of 60 cases of tuberculous epididymitis As the lesions progress extension to the opposite epididymis is common The bladder also may be affected secondarily Progressive disease may be followed by the establishment of sinus tracts perforating the scrotum and allowing the discharge of tuberculous pus to the outside

The onset of *tuberculous epididymitis* may be insidious with the development of a nodular or diffuse infiltration and this may subside and remain latent for a time or it may be acute with rapid swelling of the epididymis possibly with a serous effusion in the scrotum Later the testis may become swollen painful and even undergo softening Usually the acute inflammation subsides after several weeks leaving behind chronic lesions which may slowly progress Examination then may reveal a thickened more or less nodular epididymis if the testicle is involved it may be enlarged to twice or more its natural size The vas may be thickened and nodular and rectal examination may reveal diffuse or nodular enlargement of the seminal vesicles and prostate If any of the lesions have liquefied limited fluctuant areas may be palpable If fistulas develop tubercle bacilli may be demonstrated in the discharging pus they also may appear in the urine and the seminal fluid While rest treatment is indicated in these cases the lesions usually run a chronic course and the prognosis for ultimate healing is not good Prolonged chemotherapy *i e* for a year or more using two specific drugs such as isoniazid and PAS in combination may bring about great improvement and arrest the infection Usually the epididymis is excised if very necrotic sometimes the testicle with it

TUBERCULOSIS OF THE MENINGES AND CENTRAL NERVOUS SYSTEM

Tuberculosis of the meninges and central nervous system figures conspicuously among infected infants and children and is frequently the terminal event of fatal disease at this time of life In adults meningitis is a relatively infrequent cause of death even among those who have suffered from chronic pulmonary disease Occasionally however it is a terminal event due to hemic dissemination as resistance breaks down While leptomeningitis is the commonest manifestation the dura may contain a few scattered tubercles or may become involved by extension from an adjacent bony focus such as vertebral caries Limited lesions usually cortical may appear also in the cerebrum less often in the cerebellum or spinal cord In rare cases these may heal eventually with calcification Such tubercles may be of a chronic granulomatous character gradually increasing in size and producing the clinical manifestations of tumor the symptoms then depend on the location of the lesion

Thus tuberculous meningitis may originate from a lesion previously established in the cortex choroid plexus pia or dura or may develop as part of an acutely disseminated infection from some more remote source The distribution of the tubercles the perifocal congestion and the fibrinous exudate are characteristically basilar The regions favored are those about the circle of Willis the interpeduncular space the fissures of Sylvius and the optic chiasm Tubercles may be located in and close to the walls of arteries The contiguous brain tissue is edematous or infiltrated for a short distance

The patient may present the clinical picture of generalized miliary tuberculosis for several weeks before meningeal symptoms develop In other cases obvious chronic tuberculous disease may have been present usually in the chest Not infrequently however the patient especially if he is a child previously may have appeared perfectly well For no apparent reason the child becomes listless and irritable The appetite fails and he loses weight If he is too young to describe the headache it may be eloquently indicated as he feels or fumbles his head with his hands and by the sharp so-called "hydrocephalic cry" or the unmistakable and sustained scream of pain Vomiting is common usually sudden and often projectile sometimes it is precipitated by a change of position in bed The temperature may rise to 103 F or more in the afternoon At first the pulse may be quick but later it becomes slow in proportion to the fever The pupils initially are contracted later dilated As the terminal or paralytic phase follows that of irritation the restlessness night terrors and outcries may give way to stupor whimpering and muttering The patient may be disoriented and wander from his bed There may be clonic contractions of single groups of muscles and not infrequently general convulsions Photophobia is common and there may be strabismus and blepharoptosis Monoplegia or hemiplegia may be observed The initial constipation and urinary retention usually are followed by incontinence

Early in the disease the neck and the

muscles of the back and extremities may be sore and stiff Kernig's sign is usually positive There may be general hyperreflexia ankle and patellar clonus and a positive Babinski sign Later the muscles may become flaccid and reflexes diminished As the coma deepens the patient may execute athetoid movements Finally he becomes completely motionless the temperature varies widely and irregularly and sweating may be profuse In this unconscious state his eyes half closed and jaw agape he wearily breathes away his final hours

The natural duration of the disease varies from three to six or eight weeks occasionally deaths in children have been reported to occur in less than a week after the clinical onset Actually the disease may exist some time before symptoms become manifest occasionally during the course of generalized miliary tuberculosis a routine spinal puncture may yield fluid containing tubercle bacilli Spontaneous recovery is rare

Lumbar puncture yields fluid which is usually clear and under increased pressure occasionally it is slightly turbid or xanthochromic As the fluid stands in the tube a thin coagulum develops and tubercle bacilli may be found in this or in the sediment collected after centrifugation Otherwise culture or guinea pig inoculation usually proves positive The number of cells in the fluid usually is 25 or more per cu mm lymphocytes predominating The content of protein is found moderately or markedly increased glucose is decreased

Illingworth (1957) has reviewed his experience with diagnostic problems in miliary and meningeal tuberculosis in children and emphasizes the considerable number of cases in which the initial symptoms are vague meningismus may be absent the tuberculin skin test may be negative and the initial concentration of sugar in the cerebrospinal fluid may be 50 mg per 100 ml or more (14 per cent of his cases)

Treatment Specific chemotherapy has greatly improved the outlook of patients afflicted with tuberculous meningitis so that today when the disease is diagnosed and treated in its early stages the prospect of recovery is approximately 90 per cent When experiences of statistical value started accumulating in 1948 it became apparent that about 20 to 25 per cent of the patients treated with streptomycin or dihydrostreptomycin alone (intramuscularly and intrathecally) for periods of a few months could be expected to survive two years or longer Later the addition of PAS (orally and in some clinics intravenously) and the prolongation of such combined regimens for many months were found to improve the results substantially Then the oral administration of isoniazid which easily diffuses through normal tissue barriers into the cerebrospinal fluid in combination with streptomycin intramuscularly proved that almost all patients will survive at least for two years Most experienced clinicians now consider it unnecessary to inject streptomycin intrathecally since during the acute inflammatory phase of the disease the drug enters the cerebrospinal fluid from the blood in quantities sufficient to be of therapeutic effectiveness this also obviates the disadvantage of the local irritation caused by the drug when given intrathecally Some add PAS orally to the other two drugs but it is not clear that this contributes any additional advantage

In practice when treating adult patients isoniazid 8 to 10 mg per kg of body weight per day is given in two or three divided doses orally while streptomycin 2 0 gm daily is injected intramuscularly usually divided into two doses given eight or ten hours apart The usual dose of PAS may also be given if desired This regimen is continued up to six months the results being judged by the subsidence of symptoms and the changes in the cerebrospinal fluid which in the early weeks should be estimated at least once a week The glucose concentration is a good indicator of improvement as it rises to the normal the protein and the cells usually diminish more slowly Isoniazid is continued at the same dosage until the patient is obviously recovering at which time it may be lowered to 5 mg per kg Chemotherapy should be continued for at least a year but the dose of streptomycin may have to be reduced because of neurotoxicity If vertigo or impairment of hearing is manifested the dose may be reduced after two to six months to 1 0 gm daily in some cases 1 0 gm three times weekly or 2 0 gm every third day has been considered sufficient Des Autels and Pfuetze advocate continuing treatment for six months after the glucose and cells of the cerebrospinal fluid return to normal and prefer continuing until the protein is normal or at least falling consistently toward the end of a total of eighteen or more months of treatment The purpose of prolonged treatment is to guard against a recurrence for this has been known to take

place as long as five years after the early recovery under short term therapy *

When the disease is not treated until it has reached a late phase the recovery rate is reduced to approximately 25 to 30 per cent One of the complications which may develop in the late phase is blockage at the spinal subtentorial or basal cisternal levels from the accumulation of fibrinous inflammatory exudate It interferes with the circulation of fluid and may hinder the access of administered drugs to some areas of disease Damage to the brain may result from abnormally increased intraventricular pressure especially in children Injections of tuberculin (PPD) intrathecally have been used by Honor V Smith and her associates at Oxford for the purpose of stimulating a reaction which may help to break down the blockage and to lower the barrier between the blood and the cerebrospinal fluid A number of clinicians have administered one of the adrenal corticosteroids intrathecally to reduce the inflammatory reaction of the diseased meninges with the same end in view and have observed clinical improvement and a rapid lowering of the protein content of the fluid These measures do not appear to be necessary in cases which are diagnosed early in the disease and treated properly with isoniazid and streptomycin

Following recovery there may occasionally be some residual damage including motor palsies deafness (due mostly to streptomycin or dihydrostreptomycin given intrathecally) mental impairment and abnormal behavior These are very infrequent with present chemotherapy

TUBERCULOSIS OF THE SPECIAL STRUCTURES

The *breast* may be infected by way of the blood stream but more often by extension from an adjacent lesion such as caries of a rib or tuberculous costal chondritis The breast may be diffusely swollen and tender but more commonly localized irregular nodular swellings increasing in size appear in one or more of the segments The conglomerate tubercles usually become caseous leading to the formation of abscesses from which cutaneous fistulas may originate The infection may burrow widely under the pectoral tissues If not too extensive incision of the abscess followed by a course of combined chemotherapy may lead to healing If the glandular tissue is extensively involved mastectomy may be indicated

Tuberculosis of the myocardium while rare may occur through infection extending into it from the epicardium less often from the mediastinal lymph nodes or from the blood stream The lesions may be numerous and isolated or diffuse and caseous Alphonse described tuberculous phlebitis of the myocardial veins An extremely rare lesion is tuberculous endocarditis with valvular vegetations

Tuberculous arteritis of peripheral arteries is also rare sometimes due to the lodgment of infected emboli

Tuberculosis of the hypophysis is rare Kirschbaum and Levy studied the chronic granulomatous type which may produce the symptoms of diabetes insipidus or of pituitary cachexia (Simmonds disease)

Tuberculosis of the thyroid and the pancreas is rare and is observed only in generalized infection or as an extension from an adjacent lesion Chronic thyroiditis and less often chronic pancreatitis on a tuberculous basis are occasionally reported

Tuberculosis of the adrenals if extensive produces the Addisonian syndrome which may be rapidly progressive and fatal In these cases the adrenals are usually caseous A few tubercles may be discovered in the adrenals in generalized miliary tuberculosis and rarely old calcifications may be found

Tuberculosis of the Liver Isolated gray tubercles in the capsule or substance of the liver are not uncommon findings at the autopsy of patients who have died of pulmonary tuberculosis and they may be demonstrated in those who have never suffered from this disease In subacute and chronic forms of generalized tuberculosis particularly in young children and in Negroes numerous caseous tubercles of various sizes may be found in the liver but extensive abscess formation is uncommon Infection of the gallbladder or duct is also infrequent it is usually due to extension from an adjacent focus which may be in the lymph nodes

At Seaview Hospital Stemmerman found **tuberculosis of the bile ducts** in 3 per cent of 1500 autopsies on tuberculous subjects

For tuberculous meningitis in children the following regimen is carried out in the Children s Medical Service of Bellevue Hospital Streptomycin 1 0 gm intramuscularly for a minimum period of one month or until the cerebrospinal fluid glucose has been normal for one week thereafter 1 0 gm twice weekly isoniaz d orally 10 mg per kg daily divided into two doses for four to six weeks then 7 mg per kg sulfone (Promizole) orally 0 25 to 8 0 gm daily for two years

muscles of the back and extremities may be sore and stiff Kernig s sign is usually positive There may be general hyperreflexia ankle and patellar clonus and a positive Babinski sign Later the muscles may become flaccid and reflexes diminished As the coma deepens the patient may execute *athetoid movements* Finally he becomes completely motionless the temperature varies widely and irregularly and sweating may be profuse In this unconscious state his eyes half closed and jaw agape he wearily breathes away his final hours

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DISEASES DUE TO ATYPICAL ACID FAST BACILLI

(*Bairnsdale Disease "Swimming Pool Disease" "Yellow Bacillus" Disease*)

The study of mycobacteria from human sources was greatly stimulated by the introduction and use of specific chemotherapy for tuberculosis and this in addition to increasing our knowledge of the true tubercle bacillus has contributed a large fund of information concerning "atypical acid fast bacilli" It has long been known that a vast number of mycobacteria dwell in soil and water and on vegetable matter and that some which are harmless to man cause disease in other species of animals Hence when atypical organisms were found in the discharges of human subjects they were labelled insignificant Saprophytes such as *M smegmatis* an inhabitant about human genitalia and *M phlei* which may be ingested with food are noteworthy contaminants of certain specimens being searched for tubercle bacilli Only in recent years however has it been appreciated how often actual disease in man may be induced by mycobacteria which in some of their characteristics seem to rank between *M tuberculosis* and the saprophytes *M fortuitum* was linked with human disease by Cruz in 1938 and *M ulcerans* was reported in 1948 by MacCallum and his associates to be the pathogen in certain chronic ulcerative lesions of the skin Later a number of observers reported cases of relatively benign papules and superficial ulcers of the skin which appeared usually on the elbows following abrasions incurred while the person was swimming in an artificial pool In 1954 Linell and Norden published their study relating these infections to an organism which they called *M balnei*

While "atypical acid fast bacilli" have been implicated also in abscesses of lymph nodes they have been identified most often in recent times in connection with pulmonary disease In several series of cases the organisms have been found in the sputum of several of every 100 patients admitted to hospitals for tuberculosis and other chest conditions The pulmonary disease associated with these atypical mycobacteria may run a course closely resembling that of tuberculosis although it is usually less severe A number of fatalities have been reported several of these in cases of associated silicosis Pathologically the disease may be indistinguishable from tuberculosis with its caseous necrotic lesions and cavity formation However the infection does not often become generalized is usually only locally invasive and has a tendency to heal spontaneously Sometimes these mycobacteria have been found as secondary invaders of genuine pulmonary tuberculosis especially as it undergoes healing (Kelz Cotton and Lester) They may also appear similarly in cases of bronchiectasis and

usually the lesions were miliary or consisted of abscesses 1 0 to 20 mm in diameter

Tuberculosis of the spleen is a frequent sequel of hemic infection A few or many miliary tubercles may be found in the capsule or in the parenchyma or the organ may be enlarged and infiltrated with large caseous conglomerates the latter however is uncommon Nodular calcifications sometimes may be demonstrated roentgenographically

Tuberculosis of the ear usually is a complication of cavitary pulmonary disease The middle ear may be infected through the eustachian tube The process is subacute or chronic leading to abscess formation and slow perforation of the drum after which a chronic fistula often persists Secondary infection then may occur The mastoid may become involved but this is uncommon at least in serious degrees The diagnosis is suggested by gradually increasing painless deafness tinnitus and a feeling of fullness in the ear of a patient with cavitary pulmonary tuberculosis Perforation of the drum is usually painless also Tubercle bacilli may be demonstrated in the discharging pus The inflammation occasionally heals without perforation of the drum leaving permanent partial deafness

The *nose* may become involved in lupus vulgaris the lesions of which may extend to the mucosa Picking of the nose by a tuberculous patient is supposed sometimes to cause infection of the mucosa and development of a chronic perforating septal ulcer **Tuberculosis of the paranasal sinuses** is observed rarely

PREVENTION OF TUBERCULOSIS

The observations that some increase in resistance to tubercle bacilli may be conferred upon animals and that naturally acquired and limited tuberculous lesions have a similar effect in man have stimulated many attempts to develop means of prophylactic vaccination and passive transference of immune bodies Killed devitalized and attenuated bacilli have been tried as vaccines administered by various routes as have fractions and products of the bacilli and of the lesions caused by them It has been shown that relative immunity may develop usually in slight degree after the administration of living or dead virulent or attenuated organisms The duration of this may be a relatively few months or some years Absolute protection against subsequent virulent infection has never been proved and no plan has justified itself thus far for universal application One of the better known vaccines BCG an attenuated living strain of the bovine type of bacillus prepared by Calmette and Guerin is proved to have an immunizing capacity and the degree of this is still under study The reports of J D Aronson who conducted a test of BCG among large groups of American Indians and of R G Ferguson who vaccinated the personnel of hospitals and sanatoriums in Saskatchewan Canada are impressive because of the objective comparative methods used The tuberculosis attack and fatality rates were lower by at least 75 per cent in the groups vaccinated than in the unvaccinated For the better protection of groups especially the young who do not react to tuberculin and therefore have presumably not been infected and who are destined to have close and frequent contact with tuberculosis as in poor economic areas and in hospitals BCG has gained some favor It is generally thought however that a natural primary infection if the lesion which it produces remains limited gives greater and longer lasting relative immunity than artificial vaccination

An objection to the vaccines which are now available is the development after their inoculation into the body of tissue hypersensitivity which invalidates the usefulness of the tuberculin test for the detection of natural infection and the tracing of its source

The administration of isoniazid to infected children to test its ability to avert the occasional serious sequelae of primary tuberculosis such as meningitis has been reported by the United States Public Health Service to have definitely favorable effects

Measures which are assuredly effective for prevention include the following

- Elimination of tuberculous animals and pasteurization of milk
- Improvement of living conditions and education in personal hygiene
- Adequate medical examinations to detect lesions in their incipiency usually in the preclinical phase
- Sufficient and proper treatment of the early case to prevent excavation of the lesion and infection of "contacts"
- Isolation of the infectious case
- Rehabilitation of patients with arrested disease to prevent relapse

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Incidence and Epidemiology Known of old throughout south Asia and Africa and almost epidemic throughout Europe in the eleventh to thirteenth centuries leprosy persists today in a patchy endemic zone encircling the world largely between the thirtieth parallels of latitude but also including Japan Korea south China and South Africa Outside of these areas it does not appear to be communicable Only a handful of cases remain in Scandinavia and none in most European countries In Spain and Portugal it is still increasing in incidence In the United States leprosy is endemic in those states bordering on the Gulf of Mexico and in Hawaii

Leprosy is so difficult to acquire that it was believed for many decades to be hereditary rather than contagious yet it is so easy to acquire that nearly half the new cases are unaware of having had any contact with the disease Perhaps this paradox can best be resolved by the view that leprosy is easily acquired by contact with lepromatous persons *during transient periods of increased susceptibility* to which some persons are subject Such susceptibility may be inherited though this is unproved

The determinants of susceptibility are not known Hawaiians have seventy times the leprosy morbidity experienced by Caucasians in Hawaii and similar racial differences are reported from many other areas Children are more susceptible other things being equal than adults A family history of leprosy probably means heightened susceptibility to infection though it is not necessarily associated with low resistance to the established disease Persons with a negative Mitsuda reaction to injected lepromin (see below) are more susceptible to leprosy and they are more apt to have the lepromatous form of the disease if they do become infected than persons with a positive reaction Diet is probably unimportant

Morbid Anatomy and Clinical Features Leprosy is a disease which principally involves the skin and subcutaneous nerves It occurs in reasonably well defined types in either of which the disfigurement and deformity may be produced by the disease process itself or by the consequences of the loss of sensation or motor or trophic innervation in an affected area or part The clinical picture may also be significantly modified in the lepromatous type by the development of systemic amyloidosis or by associated infection with tubercle bacilli Because of these very considerable differences between types and groups no single clinical description will usefully depict leprosy Consequently in the present discussion the principal attention will be devoted to defining the individual manifestations in themselves quite recognizable that serve to characterize the various forms of the disease

There are two principal types of leprosy the *lepromatous* (formerly called cutaneous) type in which the patient manifests no resistance to the disease and the *tuberculoid* (formerly called neural) type in which he manifests more or less vigorous resistance to it Most cases of leprosy fall into one or the other of these two categories Transition does occasionally occur from one to the other (most often from tuberculoid to lepromatous) and a case undergoing such transition may present features of both types Nevertheless no mixed form of leprosy as such is recognized

In addition to these two relatively stable "polar types of leprosy two groups of leprosy cases are recognized the *indeterminate* (I) and the *borderline* or *dimorphous* (B) The types subtypes groups and subgroups are outlined in Table 1 and the principal distinctions among these types and groups are given in Table 2

Definitions of these types and groups adopted by the Sixth International Congress of Leprosy in Madrid in 1953 were as follows

Lepromatous type (L) A malign type especially stable strongly positive on bacteriological examination presenting more or less infiltrated skin lesions

Table 1 Types and groups of leprosy with subtypes and symbols as approved by the Sixth International Congress of Leprosy at Madrid in 1953

TYPES	GROUPS
Lepromatous (L)	*Indeterminate* (I)
Macular	Macular (I_m)
Diffuse	Pure neuritic (I)
Infiltrated	
Nodular	
Pure neuritic (?)*	
Tuberculoid (T)	*Borderline* (dimorphous) (B)
Macular (T_m)	Infiltrated
Minor tuberculoid (T_t)	Macular (?)*
Major tuberculoid (T_T)	Pure neuritic (?)*

* The bracketed question marks inserted by the Classifi ation Committee of the Congress indicate that the queried categories have not yet been described in the literature

cancer of the lung and in chronic aspirational pneumonia complicating achalasia of the esophagus

Infection with these atypical strains may produce hypersensitivity to tuberculin although the skin test usually is only weakly positive Similarly some of the strains when inoculated into animals induce not only a relative homologous immunity but also a relative heterologous immunity to other strains and to *M tuberculosis* infections The latter has been studied in connection with the vole bacillus which has been used as a vaccine for man

The disease which does not have distinctive clinical features is identified by the isolation of the sole causative organism which Runyon Buhler and Pollak and a number of other workers have observed most often to be a photochromogenic mycobacterium (cultures change from white or buff to a bright lemon yellow a few hours after exposure to a bright light according to Runyon) The organisms grow on artificial culture medium in a week or so at incubator temperature they also grow at room temperature but less rapidly Various cultural tests of virulence and growth on special media help to distinguish these mycobacteria from typical tubercle bacilli As a rule the photochromes have little or no pathogenic effects when inoculated by the standard route into guinea pigs mice may be susceptible and varied results have been noted in other animals

A characteristic of these mycobacteria is their lesser susceptibility compared with *M tuberculosis* to most of the specific antituberculous drugs Wolinsky Smith and Steenken found these organisms resistant to streptomycin and para aminosalicylic acid but somewhat susceptible to isoniazid amithiozone and a thiocarbinilide they are also susceptible to cycloserine This feature has been reported somewhat differently by others

Other strains of nontuberculous mycobacteria have been designated by Runyon as nonphotochromogens and scotochromogens These too have been found in the sputum and tissues of patients but they may be found also in healthy people and their pathogenic role is not clearly recognized The taxonomy of these atypical organisms remains to be definitely determined

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LEPROSY

Leprosy is a chronic infectious and communicable disease caused by *Mycobacterium leprae* Its principal clinical lesions occur in the cooler tissues of the body skin superficial nerves nose pharynx and larynx The distal portion of the eye and the testicles may also be damaged Disfigurement and deformity due to skin infiltration and peripheral nerve destruction of untreated patients may be extremely severe and conspicuous The disfigurement is the principal reason for the fear and loathing historically—and tragically—attached to the disease

Etiology *Mycobacterium leprae* is the cause of leprosy Discovered in 1873 by G Armauer Hansen of Norway it is an acid fast rod about the same size as *M tuberculosis* from 1 5 to 6 0 μ long and 0 2 to 0 45 μ thick It occurs in tissues singly in cigar bundle clusters and in oval aggregates 15 to 25 μ in diameter called globi *M leprae* cannot be cultivated on artificial media Though many efforts have been made (notably by Danielssen in Norway and Mouritz in Hawaii) to infect laboratory animals and even humans by injecting bacilli into them only one (by Arning in Hawaii) has been successful and in it the possibility of prior infection of the subject by ordinary means could not be excluded Apparent accidental inoculation of two Marines by tattooing was reported during World War II

Table 3 Detailed comparison of the two "polar" types of leprosy

CLINICAL FEATURES	LEPROMATOUS	TUBERCULOID
Sites of election	Skin (and nerves)	Nerves (and skin)
Distribution	Generalized usually	Localized often
Type of lesion	Leproma or nodule	Macule and plaque
Visceral involvement	Widespread subclinical	Perhaps lymph nodes
Mucous membrane lesions	Regularly and early	Nose only infrequently
Eye involvement	Often late	Very rarely
Hypopigmented macules	Occasionally early many	Frequently few
Annular plaques	Sometimes	Frequently
Erythema multiforme or nodosum	In reactions often	Not seen
Fever	In reactions usually	Rarely
Eyebrow alopecia	Often	Not seen
Gynecomastia	Sometimes late	Not seen
Symmetry of involvement	Usual	Exceptional
Nerve enlargement	Slow and symmetrical	Rapid and asymmetrical
Nerve damage	Late often partial	Early often complete
Skin anesthesia	Late but inevitable often on extremities	Early and coextensive with skin lesions
Visceral damage	Testicle only	Not seen
HISTOLOGICAL FEATURES		
General pattern	Xanthoma like macrophages and histiocytes	Sarcoid like epithelioid cell tubercles and lymphocytes
Vacuolated lepra cells	Always	Rarely in reacting cases only
Giant cells	Occasional foreign body or Touton type	Often Langhans type
Lymphocytes	Few	Abundant
Lipoid	Abundant	Minimal
Necrosis	Rarely	Caseation rare in skin common in nerves
Nerve changes	Fibrosis structure well preserved	Obliteration of normal architecture
Visceral amyloidosis	Common late	Not seen
BACTERIOSCOPY		
Acid fast bacilli (*M leprae*)	Abundant except in long treated or burned out cases	Rare or lacking except during reactions never abundant
SPECIAL TESTS		
Lepromin (Mitsuda) reaction	Negative	Positive
Serological tests for syphilis	Biological false positive in half of cases	No false positives
Hyperglobulinemia	Usual	Exceptional
Erythrocyte sedimentation rate	Elevated especially during reactions	Usually normal
CLINICAL COURSE		
Course untreated	Progression fatal in 10 to 20 years usually	Spontaneous recovery as a rule in 1 to 3 years
Course treated with sulfones	Slow regression (3 to 8 years)	More rapid regression
Intercurrent tuberculosis	Common in untreated cases	Rare
Transition to other type	Rare even under treatment	Occurs in some severe and reacting cases
Contagiousness for others	Definitely established	Slight or nil
Disposition of case	Isolation necessary in endemic areas until bacilli disappear	Isolation unnecessary except during reactions

Table 2 Fundamental distinctions among the two types and two groups of leprosy cases.

	LEPROMATOUS Type	BORDERLINE Group	INDETERMINATE Group	TUBERCULOID Type
Clinical Features				
Character and prognosis	Stable malign and progressive	Unstable either progressive or regressive	Unstable often regressive may progress to either polar type	Stable benign, usually regressive
Skin lesions	*Lepromas papular or nodular**	*Plaques often annular*	*Pale or pink macules*	*Pale macules or raised plaques often annular*
Nerve damage	Slow and symmetrical	Generally more rapid than in lepromatous symmetrical	Usually only slight and symmetrical	Sudden severe asymmetrical
Bacterioscopy	Abundant bacilli	Many bacilli	Few bacilli if any	Usually no bacilli except during reactions and in nerves
Histology	Xanthoma like	Sarcoid like but with some lipid filled cells dimorphous	Banal round-cell infiltration	Sarcoid like
Lepromin reaction	Negative	Negative or weakly positive	Negative or weakly positive	Positive often strongly so

* Except in Lucio s pure diffuse lepromatous leprosy in which no lepromas occur This form is very rare outside of Mexico and Costa Rica

and negative to lepromin The peripheral nerve trunks become manifestly involved as the disease progresses habitually in symmetrical fashion and often with neural sequelae in advanced stages

Tuberculoid type (T) Usually benign markedly stable generally negative on bacteriological examination presenting in most cases erythematous skin lesions which are elevated marginally or more extensively positive to lepromin Sequelae of peripheral nerve trunk involvement may develop in a *certain proportion of cases and this may give rise* to serious and disabling deformity This frequently appears to occur as a result of extension from or through cutaneous nerve branches rather than of systemic dissemination and consequently it is often asymmetrical and unilateral

The tuberculoid type was subdivided (Table 1) into *macular* (T_m) *minor tuberculoid* (T_t) and *major tuberculoid* (T_T) subtypes characterized by flat pale anesthetic macules pebbled erythematous slightly raised plaques and markedly elevated and thickened erythematous plaques respectively The T variety is precisely that originally known as "maculoanesthetic Wade believes that it should still be so designated on the ground that patients with such flat lesions have not developed enough resistance to warrant being classified as tuberculoid

Indeterminate group (I) A benign form relatively unstable seldom bacteriologically positive presenting flat skin lesions which may be hypopigmented or erythematous *the reaction* to lepromin negative or positive Neuritic manifestations more or less extensive may develop in some cases which have persisted *as of* this group for long periods The indeterminate group consists essentially of "simple macular" cases These cases may evolve toward the lepromatous type or the tuberculoid type or may remain unchanged indefinitely

Borderline (dimorphous) group (B) A malign form very unstable almost always strongly positive on bacteriological examination with the lepromin reaction generally negative This group may arise from the tuberculoid type as a result of repeated reactions and sometimes evolves to the lepromatous type The nasal mucosa is generally bacteriologically negative The skin lesions are usually seen as plaques bands nodules etc with a regional distribution similar to that of lepromatous leprosy except for [usually but not always] conspicuous asymmetry The ear lobes are likely to present the appearance of lepromatous infiltration The lesions frequently have a soft or succulent appearance and their periphery slopes away from the center and does not present the clear cut well defined margins seen in the tuberculoid type the lesions are therefore liable to be mistaken for lepromas The surface of the lesions is generally *smooth with a* shiny appearance and a violaceous hue sometimes (in light skins) with a brownish (sepia) background

A detailed catalogue of the many contrasts between the two polar types of leprosy—lepromatous and tuberculoid—is given in Table 3

Reactions More or less transitory states of exacerbation or reactivation known as reactions may occur once or repeatedly in all forms of leprosy In lepromatous leprosy these are known as *lepra reactions* and two principal forms are recognized The ordinary lepra reaction consists of aggravation of existing skin lesions development of new ones and usually fever neuralgia and malaise or prostration lasting *for* hours days or weeks This may or

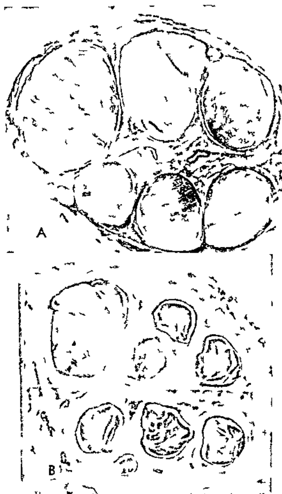


FIG 34 Lepromatous leprosy of ulnar nerve at the elbow (A) with normal nerve (B) cut at same level for comparison Note characteristic preservation of fairly normal architecture The great thickening is due chiefly to thickening of the fibrous sheaths (Arnold H L Jr Modern Concepts of Leprosy Springfield Illinois Charles C Thomas 1953)

single edged safety razor blade is inserted 3 or 4 mm deep into a pinched up fold of involved skin or even uninvolved skin *e g* an ear lobe It is then rotated about an axis perpendicular to the skin surface so that its edge scrapes the side of the cut and a small drop of tissue pulp and lymph is obtained Blood does not interfere seriously This drop is deposited (*not* spread thin) on a clean slide dried and stained by the Ziehl Neelsen method destaining with preferably Gabbett s solution The carbol fuchsin should be used cold not warm for fifteen minutes The preparation should not be subjected to decolorization too long because *M leprae* is much less acid fast than *M tuberculosis*

The standard Ziehl Neelsen staining procedure is not sensitive enough to be used on paraffin sections of tissue if bacilli are at all scarce Wade s modification of the Fite Faraco stain (Am J Path 28 157 1952) should be used to prevent defatting the bacilli

In the absence of bacilli a suspicion of leprosy needs confirmation by demonstration of nerve damage Such damage may consist of anesthesia or anhidrosis (usually coextensive with a skin lesion in tuberculoid cases often on feet or hands in lepromatous) thickening of superficial nerves muscular weakness or atrophy especially in the face and hands or histological changes in a biopsy specimen

Leprous neuritis often produces sensory dissociation similar to that seen in syringomyelia sense of touch may be preserved but that of heat and cold or pain or both may be lost Each should be tested separately Palpation of the great auricular nerves where they cross the sternocleidomastoid muscles of the ulnar nerves just above and behind the internal humeral epicondyles or of the peroneal nerves behind the heads of the fibulas may reveal thickening nodularity stiffness or tenderness any or all of which are extremely suspicious of leprous neuritis Drooping of one or both lower eyelids or oral commissures or weakness of elevation of one eyebrow may disclose the patchy weakness of facial muscles which Monrad Krohn has said is the most distinctive single neuro



FIG 35 Tuberculoid leprosy of great auricular nerve The nerve was almost 1 0 cm thick (normally 2 0 or 3 0 mm) Histologically there was complete obliteration of normal architecture with replacement by epithelioid cell tubercles and some caseation necrosis (Arnold H L Jr Modern Concepts of Leprosy Springfield Illinois Charles C Thomas 1953)



FIG 32 Lepromatous leprosy in a young boy Note symmetrical involvement and predilection for cooler acral parts brows ears nose cheeks chin and fingers Of interest also are madarosis (loss of eyebrows) and the burn scar on his anesthetic left hand (Arnold H L Jr Modern Concepts of Leprosy Spingfield Illinois Charles C Thomas 1953)



FIG 33 Annular plaque of major tuberculoid (T_T) leprosy which is verging on the borderline (B) variety as is shown by the loss of sharpness and steepness of the outer margin Such a lesion is always anesthetic (Arnold H L Jr Modern Concepts of Leprosy Springfield Illinois Charles C Thomas 1953)

may not be accompanied by erythema multiforme of either the ordinary or bullous variety If as frequently happens it takes the form of erythema nodosum the reaction is referred to as *erythema nodosum leprosum* this pattern is most often seen during sulfone therapy and is generally believed to carry with it a relatively good prognosis in regard to the leprosy

In tuberculoid or borderline leprosy reactions consist of aggravation of previous lesions or the appearance of succulent elevated new plaques painful swellings of nerves may occur *M leprae* may become quite numerous in the lesions and the lepromin reaction may decrease in intensity Fever and constitutional symptoms (including erythema multiforme) do not occur in tuberculoid cases

Diagnosis An advanced case of leprosy with the combination of skin lesions and obvious nerve lesions should be readily recognized by the reasonably alert physician It is in the early cases in which the nerve involvement is not readily apparent that the diagnosis of leprosy may be missed In certain forms of the disease the diagnosis can be definitely established by demonstration of the presence of *M leprae* in material obtained from the patient s lesions It is important to realize however that a clinical impression or suspicion of leprosy as such cannot be *excluded* by any one diagnostic procedure A suspicion of *lepromatous* leprosy can be excluded by finding no acid fast bacilli in the lesions but such a negative finding will not exclude the indeterminate or tuberculoid variety A suspicion of *tuberculoid* leprosy can be eliminated by excluding all evidence of nerve damage in the lesions but such a finding will not exclude the indeterminate or lepromatous type

Nasal scrapings though they will show acid fast bacilli in perhaps one third of early lepromatous cases and in all advanced ones may be either positive or negative in either type of leprosy and cannot be relied upon either to confirm or to exclude the diagnosis Nonpathogenic acid fast diphtheroid bacilli indistinguishable from *M leprae* may be found even in a normal nose

A simple and trustworthy method of looking for bacilli in skin lesions is Wade s "scraped incision" procedure The point of a scalpel or better still the corner of a

are outlined in Table 4 The duration of *treatment in tuberculoid cases is determined* by the clinical response since bacilli are usually lacking from the start a clinically satisfactory result is likely to require a year *or two In lepromatous cases treatment is* continued until the skin lesions and nasal mucosa are healed and virtually devoid of acid fast bacilli—usually at least two or *three years in early cases and perhaps as* long as six or eight years in heavily involved cases Maintenance therapy for prevention of relapse is still an unsettled question Ericson has shown that it is necessary for some lepromatous cases and it is probably advisable for most Patients with a strongly positive reaction to lepromin however usually remain well indefinitely without maintenance therapy

Reactions are mild and infrequent with small doses of sulfones Moderate over dosage may cause headache anorexia nausea dizziness insomnia or tachycardia Anemia which may occur at any dose level is the commonest potentially serious reaction and should be watched for by hemoglobin determinations weekly and later monthly Toxic psychosis agranulocytosis hematuria or erythema nodosum may be seen with larger doses of any sulfone and require interruption of treatment or reduction of the dose

In the event of complete intolerance for even small doses of sulfones amithiozone *is probably the best substitute The dose is* 25 mg a day initially increased slowly to a maximum of 100 to 150 mg a day by mouth Dihydrostreptomycin 1 0 gm intramuscularly three times a week is much less effective according to most observers though controlled studies over short periods in the Philippines and South Africa under Doull s direction suggest that it is almost as good as the sulfones Isoniazid and para aminosalicylic acid are not reliable in their effects upon the disease

During lepra reactions bed rest is indicated and acetylsalicylic acid and antihistaminics may be helpful The sulfone dosage must be sharply reduced as a rule *Erythema multiforme ordinary or bullous* or erythema nodosum may be controlled with corticotropin or adrenal steroids in the usual doses

Keratitis iritis or iridocyclitis may occur in lepromatous cases and may require treatment with 1 per cent hydrocortisone drops or oral hydrocortisone or prednisolone *Atropinization is indicated for iridocyclitis* In advanced cases eyelid paralysis may lead to exposure keratitis

Although lepromatous neuritis is slowly progressive tuberculoid leprous neuritis may cause rapid swelling of one or more nerve trunks sometimes with such intense and persistent pain as to require surgical decortication of the nerve involved Nerve abscesses which occur rarely may require incision and drainage

Orthopedic procedures aimed at rehabilitation of patients with claw hand resulting from ulnar neuritis or foot drop from peroneal palsy differ in no essential respect from those devised for similar lesions due to other diseases

Social psychological and economic rehabilitation may present the most difficult and surely the most important problem of all A physician who must deal with even a single case of leprosy should read Perry Burgess *Who Walk Alone* and *Born of Those Years* He should also read George Fite s article entitled Leprosy Society and *Hansen s Disease" in the October December* 1956 issue of the *International Journal of Leprosy* Fear of leprosy is where you find it and it is not necessarily eradicated by education *Nevertheless it is the physician s* responsibility to relieve fear of the disease in the patient and the family so far as he can by calm and sympathetic explanations—and when the patient is well to do what he can to help him resume as nearly normal a life as possible

Prevention Prevention of leprosy involves primarily the recognition and isolation of bacteriologically positive cases in endemic areas Home isolation may well be ade

Table 4 Principal antileprosy drugs and their dose schedules

	INITIAL DOSE	USUAL MAXIMUM DOSE	ROUTE
4 4 Diamino diphenyl sulfone (Avlosulfon [Ayerst])	25 mg 2 or 3 times per week	100 mg per day *500 mg* per week (in oil)	Oral or intramuscular Intramuscular
Sulfoxone sodium (Diasone [Abbott])	0 3 gm 3 to 6 times per week	1 0 gm daily	Oral only
Glucosulfone sodium (*Promin* [Parke Davis])	0 5 gm 3 to 6 times per week	1 0 to 5 0 gm per day	Intravenous only

logical sign of leprosy Contracture of a fifth finger or flattening of a hypothenar or thenar eminence or the grooving produced by atrophy of the interosseous muscles of the hands may betray the presence of leprous ulnar or median neuritis Actual claw hand deformity or foot drop may ultimately occur

Biopsy of a thickened great auricular nerve or of other skin nerves which serve no important motor function is a practicable procedure of value if a diagnostic biopsy of skin is not possible The histological changes are usually characteristic and in tuberculoid leprosy bacilli are much more readily found in the nerves than in the skin

Roentgenograms of hands and feet may show concentric absorption of phalangeal or metatarsal shafts a characteristic "trophic" lesion which leads ultimately to loss of continuity of the bone and shortening of digits or of the whole foot Rarely diabetic peripheral neuritis may produce such changes but without anesthesia Dropping off of digits is a myth

Painless trophic plantar ulceration identical with that seen in tabes dorsalis and in syringomyelia may also occur Such ulcers are not primarily leprous and no bacteriological or histological evidence of leprosy is to be found in them They often lead to osteomyelitis of metatarsal bones

Histamine Test A *de*pigmented macule unless it is an actual scar is never a manifestation of leprosy A *hypo*pigmented macule however may be If such a macule is not anesthetic to heat or cold or to touch or pain and no other evidence of nerve damage is found and no bacilli are present then the most sensitive tests of nerve damage should be applied before concluding that the lesion is not leprous The simplest of these is the histamine test A shallow pinprick is made through a drop of 1 1000 histamine phosphate solution inside or at the edge of the macule The flare around the resulting wheal will be lacking inside a leprous macule In deeply pigmented skins this test is difficult or impossible to interpret and the Mecholyl sweating test may be used This can be done by injecting 0 1 ml of 1 per cent methacholine chloride solution intradermally inside or at the margin of the macule and observing by any of several techniques the distribution of the resulting sweat response Sweat glands within a leprous macule will not respond If they fail to respond in the normal surrounding skin as well the result is obviously inconclusive

Lepromin Test The lepromin test is performed by the intradermal injection of 0 1 ml of a boiled or autoclaved gauze filtered suspension of *M leprae* and human tissue prepared by grinding lepromatous granulation tissue in a mortar and suspending it in saline solution Mitsuda reported in 1919 that such an injection was followed by no reaction in patients with lepromatous leprosy but that in tuberculoid cases an inflammatory nodule resulted reaching its height in about three weeks and sometimes ulcerating Fernandez later described a forty eight hour Mantoux like reaction fairly well correlated with the Mitsuda response A positive lepromin reaction does *not* denote the presence of leprosy It is positive in roughly half the population in many areas in which leprosy does not even occur It apparently denotes resistance to leprosy Its high correlation with a positive Mantoux reaction especially in persons without leprosy and the regularity with which BCG vaccine causes negative Mitsuda reactors to convert to positive suggest a relationship with exposure to tuberculosis which has not yet been explained or even fully evaluated The use of BCG vaccine to protect susceptible contacts against leprosy is now undergoing extensive experimental testing especially in South America

Prognosis Without treatment patients with lepromatous leprosy tend to suffer steady progression of their disease and to die of tuberculosis amyloid nephrosis intercurrent infection or leprosy within about fifteen years from the time the disease is first recognized Patients with tuberculoid leprosy untreated tend to recover completely except for residual nerve damage within a year or two if only one or a few annular plaques are present If their skin lesions are numerous and widespread the disease may run a rather protracted course with repeated relapses but the patient will still tend to recover completely if the lepromin reaction is strongly positive

With chemotherapy virtually all patients experience immediate arrest of the disease and steady improvement Recovery (except for residual nerve destruction) is usually complete in a year or two if bacilli were initially few or absent or in three to perhaps six or eight years if bacilli were initially abundant and the lesions widespread

Treatment The sulfones have almost entirely replaced chaulmoogra oil and its esters in the specific chemotherapy of leprosy The dosage and method of administration of the most commonly used sulfones

Symptoms and Course of the Disease *Anemic Form (Oroya Fever)* The incubation period is believed to be fourteen to twenty one days In severe cases the onset is sudden with intermittent fever ranging to 104° F progressive pallor emaciation prostration rapid pulse and dyspnea Muscle and joint pains nausea vomiting diarrhea headache and insomnia are also common symptoms and delirium and coma are apt to be terminal manifestations A petechial cutaneous eruption occasionally appears during the febrile period The erythrocyte count may fall from normal to less than 1 000 000 per cu mm in four or five days more rapidly than in any other condition exclusive of actual hemorrhage Examination of alcohol fixed Giemsa stained blood films shows bartonellae in the erythrocytes in large numbers 90 per cent of the cells frequently containing from one to fifty or more organisms (Fig 36) Many reticulocytes and nucleated erythrocytes are present in the blood In the severe form of the disease the mortality is 90 to 95 per cent Secondary infection particularly with organisms of the salmonella group has been emphasized as an important factor in fatal cases The average duration of this anemic stage of the disease is from one to three weeks occasionally the condition of the patient remains critical for a period of eight to ten weeks Convalescence is accompanied by a disappearance of the organisms from the erythrocytes and rapid blood regeneration but blood cultures may be positive for many months after apparent recovery

Cutaneous Form (Verruga Peruviana) This form of the disease characterized by cherry red hemangioma like cutaneous nodules may follow the severe anemic form or may occur in patients who have had no previous symptoms Intermediate cases are also frequently seen in which there is moderate anemia with rare bartonellae in the erythrocytes slight or no fever and only a few days of malaise followed weeks or months later by the typical cutaneous eruption The appearance of the cutaneous nodules may be immediately preceded by a few days of moderate fever with joint pains

The cutaneous nodules (verrugas) are commonly 2 to 10 mm in greatest diameter but range up to 3 or 4 cm They may be single or extremely numerous These are most numerous on the head hands feet and lower arms and legs and are rare on the thighs abdomen or lower chest Occasionally they are seen in large numbers on the mucous membrane of the mouth and pharynx They are ovoid or spherical and usually half buried in the subcutaneous tissue and covered with thin bluish epidermis which often breaks down leading to ulceration and secondary infection Healing occurs with little or no cicatrization after a period of several weeks The cutaneous stage has no mortality *per se* The possible complications are hemorrhage and local secondary infection neither of which is apt to be serious

Diagnosis The diagnosis is made from a history of residence in an infected area and on the clinical pictures Finding bartonellae in the erythrocytes in blood films establishes the diagnosis in the anemic stage In the cutaneous stage a nodule may be excised and bartonellae may be demonstrated in the endothelial cells Blood cultures in Leptospira medium are positive in both stages Rarely the cutaneous nodules may appear a year or more after an uneventful visit to an infected area Yaws which may simulate verruga peruviana can be differentiated by the demonstration of the specific organism

The anemia is of the macrocytic type and the color index may be greater than one The erythrocytes increase in both volume and hemoglobin content but since the increase in volume is proportionally greater the anemia is classified as hypochromic Anisocytosis poikilocytosis and polychromatophilia are constantly present Normoblasts are numerous and megaloblasts are usually present Reticulocytes may constitute more than 50 per cent of the erythrocytes The leukocyte count is variable but often high and many imma



Fig 36 Carrion s disease Giemsa-stained blood films showing *Bartonella bacilliformis* in erythrocytes Both bacillary and coccoid forms are seen

quate *especially if children are not concerned* Bacteriologically negative persons —*and any cases outside of endemic areas*— apparently constitute little or no risk to others and need not be isolated If *home* isolation is not practical bacteriologically positive patients should *either move to a nonendemic area for treatment or (in the continental United States)* be admitted to the U S Marine Hospital at Carville Louisiana

There is evidence that persons with a *positive* lepromin reaction run much less risk of acquiring leprosy than persons with *a negative one It may well be that one* should perform BCG vaccination upon lep*romin negative* persons if they are exposed to leprosy in order to induce a positive *skin test* Experimental evidence suggests that the induced positive test is accom*panied* by resistance just as the naturally positive one is

Isolation should be maintained until the patient is bacteriologically negative or virtually so Most leprosy institutions have established policies in regard to the requirements for release of patients from isolation

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Bartonellosis

(Carrion s Disease Oroya Fever Verruga)

Definition Carrión s disease is a specific arthropod borne infection caused by a minute rickettsia like microorganism and characterized clinically by an acute febrile anemic stage (Oroya fever) followed several weeks later by a nodular cutaneous eruption (verruga peruviana) Either of these stages may be inconspicuous or apparently absent and for this reason the *two clinical pictures* were originally regarded as separate diseases

Distribution and Epidemiology The disease has been found chiefly in narrow valleys *in the Andes Mountains* at altitudes between 2000 and 9000 feet It has been largely confined to Peru with a few cases *in Ecuador and Bolivia but in 1939* a serious outbreak was reported in Colombia suggesting that the distribution may be more widespread than has been supposed The distribution of the disease corresponds in general to the habitat of its probable sandfly vectors *Phlebotomus noguchii* and *P verrucorum* but *in Colombia lice* and ticks have been suggested as vectors Many natives of the infected areas have asymptomatic infections revealed only by blood culture Severe epidemics in Peru have often been associated with the importation of railroad workers from noninfected regions *A reservoir for the infection* in lower animals has been suspected but not found

Etiology The etiological agent was first seen in the erythrocytes in the anemic form of the disease by Barton in 1909 and was named *Bartonella bacilliformis* by Strong and his coworkers in 1915 It was cultivated in Noguchi s leptospira medium by Noguchi and Battistini in 1926 Noguchi s original evidence of the etiological identity of Oroya fever and verruga peruviana was further confirmed by new methods of approach by the Harvard 1937 Expedition to Peru and the unity of the two conditions must be considered as established

Rats dogs and a number of other mammals suffer from latent bartonella infections which after splenectomy evolve into a severe anemia comparable to Oroya fever Cutaneous lesions do not occur in lower animals Except for the transmission of human bartonella infection to monkeys *each species of bartonella appears to* be completely specific for the species of animal from which it is recovered

Morbid Anatomy Postmortem studies of fatal cases of the anemic form of the disease show pallor enlargement of the spleen and lymph nodes and a megaloblastic hyperplasia of the bone marrow The endothelial cells lining small vessels in the lymph nodes spleen liver bone marrow adrenals kidneys and many other organs are packed with small bacillary and coccoid organisms (bartonellae) often occurring in clusters Microscopically the cutaneous nodules have the appearance of rapidly growing *capillary hemangiomas Bartonellae may* be demonstrated within the endothelial cells with suitable technique

THE MYCOSES

Actinomycosis

Definition Actinomycosis is a chronic granulomatous infection caused by *Actinomyces bovis* The disease is characterized by the development of numerous abscesses which break down and develop multiple sinuses

History In 1877 Bollinger found the ray fungus in a disease of cattle known as 'lumpy jaw' it was named *Actinomyces bovis* by Harz J Israel in 1878 discovered the disease in man and pointed out the identity of the two infections Lord 1910 demonstrated that *Actinomyces* pathogenic for guinea pigs could be found in the gums and tonsils of apparently normal persons

Etiology Actinomycosis is widely disseminated and is the most common of the highly fatal mycoses The disease occurs most frequently in males

Mycology The organism occurs in pus or tissues as lobulated or spherical granules which vary in size from minute particles to forms about 1 mm in diameter Pure cultures are readily obtained from material aspirated from unopened abscesses but isolation is difficult from draining sinuses because of the overgrowth from contaminating bacteria *Actinomyces bovis* is anaerobic and grows best at 37 C in glucose agar in a zone 5 to 10 mm below the surface

Immunology Not much is known about the serological reactions of patients with actinomycosis

Pathology Actinomycosis may develop in any part of the body A granulomatous lesion is produced which is surrounded and intersected by new connective tissue The local lesions spread by direct extension through the connective tissue rather than by way of the lymphatics although metastatic lesions appear in various parts of the body as a result of showers of infected emboli

Clinical Manifestations The clinical symptoms vary somewhat depending upon the part of the body involved

Cervicofacial actinomycosis accounts for more than 50 per cent of all instances of the disease Infection takes place through the mucous membranes of the gums mouth pharynx or larynx The whole infected area becomes indurated or "wooden in consistency and extends beyond the apparent area of inflammation The overlying skin has a dark red or purplish color and a lumpy uneven surface As the infection spreads to the surface multiple sinus tracts appear With internal extension the bones of the skull and even the meninges and brain may be involved Trismus develops when the muscles of mastication are involved and dyspnea when there is pressure on the larynx The lymph nodes of the neck usually are not involved Pain is not a prominent feature and the patient s general health is not much affected so long as the disease remains localized in the area of the face and neck

Thoracic actinomycosis occurs in about 15 per cent of the cases and produces cough sputum increasing dyspnea slight fever loss of weight and strength night sweats pallor and emaciation The sputum contains blood in about half the cases and sometimes a fatal hemoptysis occurs Pleural pain is common and effusions not infrequent After the disease has reached the pleura it usually involves the thoracic wall extends through the subcutaneous tissues and produces localized areas of induration with suppurating foci and multiple sinus formation There may be extension to the mediastinum esophagus and pericardium

Abdominal actinomycosis is found in 20 to 30 per cent of the cases and represents a highly fatal form of the disease The earliest signs are usually in the ileocecal region and are associated with the development of an indistinct irregular mass which is not painful as a rule and shows no characteristic features This may be the first manifestation of the disease or it may be preceded or accompanied by fever chills night sweats intestinal colic and vomiting As the disease progresses there is usually involvement of the liver and spleen and symptoms of cystitis and pyelonephritis may appear Jaundice may be present Involvement of the central nervous system may occur in the terminal stages

ture forms are usually seen The plasma volume is increased

The blood bilirubin is usually moderately increased but neither hemoglobinemia nor hemoglobinuria is present even in the severely anemic cases

Treatment In the acute febrile form of the disease penicillin streptomycin chloramphenicol and tetracycline have all been used individually with apparently good results The criteria for effectiveness are a rapid fall in temperature to normal levels and the disappearance of the bacillary forms of bartonella from the circulating erythrocytes within forty eight hours coccoid forms may persist several days longer Evaluation of chemotherapeutic results is rendered difficult by the small number of cases in each series and by the fact that treatment has usually been initiated at a relatively late stage when it is difficult to exclude the possibility of spontaneous improvement

At present writing the effectiveness of chloramphenicol (average dosage 17 gm in five days in divided doses) seems best documented It should be noted that Cuadra believes this drug to be effective primarily because it cures or prevents the concomitant or subsequent salmonella infection (which he believes to be the most important cause of death) while Urteaga and Payne stress the resulting rapid disappearance of bartonellae from the blood followed by a prompt reticulocyte response Chloramphenicol may be given intravenously in comatose patients Chemotherapeutic treatment of salmonellosis and other secondary infections should be guided when possible by blood cultures and drug susceptibility tests and the calculated risk of bone marrow depression by chloramphenicol should be kept in mind Iron should be given during convalescence

Transfusions should be given when indicated by the clinical picture and by critically low erythrocyte counts and hemoglobin levels General symptomatic and supportive treatment including the control of electrolyte balance in severely ill patients is obviously important

The cutaneous stage rarely requires treatment except for general cleanliness Excision of large necrotic secondarily infected nodules occasionally may be indicated but probably does not improve the final cosmetic result

Prevention Fine mesh screening (25 to 30 squares per inch) and DDT are most effective against the sandfly These measures are most important during the night when sandflies are active

HENRY PINKERTON

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Blastomycosis

Definition Blastomycosis is a chronic granulomatous disease which may be confined either to the skin or lungs or disseminated throughout the body

History The disease was first described by Gilchrist in 1894 and by Gilchrist and Stokes in 1896 It is found frequently throughout the western hemisphere but only sporadically in Europe It is usually called American blastomycosis or Gilchrist's disease and should not be confused with European "blastomycosis" which is caused by *Cryptococcus neoformans (Torula histolytica)*

Etiology Blastomycosis is prevalent in the Chicago area Louisiana Tennessee North Carolina and other parts of the country The disease is nine times as frequent in males as in females

Mycology The morphological studies of Conant and the serological investigations of Martin show that all strains of *Blastomyces dermatitidis* are morphologically and antigenically identical Sputum pus or biopsy material should be streaked heavily on Sabouraud's slants and on blood agar plates which contain antimicrobial drugs The slants are kept at room temperature but the blood agar plates should be incubated at 37 C The primary growth may be slow and cultures should be watched for two or three weeks On blood agar the colonies are small waxy and wrinkled and when emulsified in water and examined fresh under the microscope show typical budding double-contoured yeastlike forms (7 to 10 μ) identical in appearance with those found in the lesions

Immunology Many patients acquire a sensitivity to the products of *B dermatitidis* and give a skin test analogous to the tuberculin reaction Martin found that patients with extensive involvement usually show a positive complement fixation when the whole yeast organism or certain of its extracts are used as the antigen The test is negative when the lesions are small or well localized and becomes negative in the systemic cases after recovery

Pathology The primary skin lesions may be of a superficial verrucous type with little ulceration or gummatous with open craters The multiple subcutaneous abscesses found in the systemic type of blastomycosis are analogous to cold abscesses in tuberculosis When the disease spreads from the skin bones or other organs to the lungs it produces the appearance in the roentgenogram and at necropsy of a miliary hematogenous tuberculosis

The characteristic budding organisms are found in the giant cells in the granulation tissue between the cells and about the edges of the necrotic areas

Clinical Manifestations *Cutaneous blastomycosis* occurs most frequently on the face neck or extremities The primary lesion usually begins as a small reddish papule or papular pustule which slowly increases in size and is soon capped with a crust There is epithelial hyperplasia giving the lesion a verrucous appearance Minute epidermal abscesses appear about the edges of the lesions and some lesions break down to form deep crater like ulcers with hard raised edges The subjective symptoms are mild pain is minimal and the patches are not sensitive to pressure The regional lymph nodes usually are not enlarged and the general health of the patient is not impaired so long as the disease is confined to the skin

Systemic Blastomycosis Patients with primary pulmonary blastomycosis have fever night sweats loss of weight cough sputum which is frequently bloody leukocytosis increased erythrocyte sedimentation rate and physical and roentgenographic evidence of extensive pulmonary disease The lesion usually is incorrectly diagnosed as pulmonary tuberculosis but it may be mistaken for primary bronchogenic carcinoma Sinus formation is rare as long as the disease is confined to the lungs but in the systemic cases in which there are multiple lesions of the bones and involvement of the internal organs it is frequent and characteristic

Diagnosis Cutaneous blastomycosis is readily diagnosed by its characteristic lesions but the diagnosis should be confirmed by finding the organisms in the pus expressed from the small abscesses in the edge of the lesion by culture or by biopsy In the systemic form the organisms can usually be grown from the sputum or from pus aspirated from a subcutaneous lesion A positive complement fixation reaction is diagnostic but a negative result does not eliminate the possibility of the disease

Prognosis The prognosis is good in cutaneous blastomycosis but poor for the pulmonary and systemic forms of the disease Martin and Smith found that 92 per cent of the patients with the generalized form of the disease had died within two years The prognosis in the pulmonary form can be improved by early diagnosis and prompt and adequate treatment

Treatment. The introduction of stilbamidine and 2 hydroxystilbamidine has revolu

Diagnosis The diagnosis is based on the clinical syndrome the finding of the sulfur granule in the exudate or lesion or the cultivation of the organism Biopsies of the sinus tract should be made when direct examination of the exudate fails to show granules Frequent and repeated study of the exudate both in fresh preparations and with the Gram stain is imperative Cultures are reliable in the yeastlike mycoses but not in actinomycosis The cervicofacial forms must be differentiated from glanders tularemia tuberculosis and osteomyelitis The pulmonary form simulates tuberculosis pulmonary abscess tularemia and other mycoses The abdominal form may be mistaken for chronic appendicitis amebiasis typhoid fever carcinoma of the intestines tuberculosis liver abscess psoas abscess and sarcoma of the retroperitoneal tissue or of the iliac bones

Prognosis The prognosis is best in the localized skin and cervicofacial types and becomes progressively worse with the thoracic abdominal generalized and neurological types

Treatment The general resistance of the patient should be supported as in tuberculosis by rest in bed and good food supplemented by vitamins and fruit juices

Penicillin is the most effective drug for the treatment of actinomycosis The sulfonamides are almost as good and can be substituted for penicillin when the patient is discharged from the hospital for a six month period of continuous therapy Potassium iodide should be given concurrently with sulfonamides during the convalescent phase of therapy The broad spectrum antimicrobial drugs are effective but are expensive and dangerous when administered for weeks or months Surgical evacuation of pus necrotic bone and destroyed lobes is an essential part of therapy

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Nocardosis

Definition Nocardosis is a chronic granulomatous disease caused by *Nocardia asteroides* and related species

History This organism was isolated by Eppinger in 1890 and called *Cladothrix asteroides* Subsequent isolates by other workers were called *Streptothrix Actinomyces* or *Proactinomyces* thereby creating the confusion of names in the older literature

Mycology The organism occurs in pus or tissues as gram positive branching filaments which are usually acid fast Unlike Actinomyces Nocardia grows readily on all usual laboratory media at either room or incubator temperature under aerobic conditions

Pathology Abscess formation occurs earlier and somewhat *more frequently in* nocardosis than in actinomycosis

Clinical Manifestations The clinical picture *may be identical with that* of actinomycosis but primary involvement of the cervicofacial area and the abdominal organs is somewhat less frequent and infections of the lungs and feet more frequent The course of the disease is usually more fulminating and small pulmonary lesions often metastasize to the brain

Prognosis The prognosis is very grave unless the infection is diagnosed correctly and treated promptly

Treatment Penicillin is not effective even in daily doses of 10 000 000 to 20 000 000 units *In contrast sulfadiazine and other* sulfonamides seem to be specific Four to 6 0 gm of sulfonamide should be given *daily to obtain* blood concentrations of 8 to 12 mg per 100 ml The broad spectrum antimicrobial drugs are palliative rather than curative but may be necessary to control secondary infections Surgery and iodides are not often required but should be used when indicated

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may be found anywhere in the southwestern United States and appears to be spreading eastward Thousands of soldiers in army camps in the Southwest contracted the benign primary infection and a few of them developed severe granulomatous disease five to eight years after the initial infection The disease occurs at all ages from three months to seventy years but is most prevalent between the ages of twenty five and fifty five In one series of 211 cases 83 per cent of the patients were males

Etiology The causative agent is *Coccidioides immitis* Emmons has shown that the organism is present in rodents in the endemic area and Davis Smith and Smith isolated the fungus from the soil The organism may be introduced into man through a scratch or abrasion of the skin although the more usual method is inhalation which produces an atypical type of bronchopneumonia The disease is not transmitted directly from man to man but laboratory infections occur frequently from the accidental inhalation of arthrospores from cultures

Mycology *Coccidioides immitis* multiplies in the tissues by endosporulation The organism is a spherule with a thick hyaline capsule varies from 11 to 70 μ in diameter and contains from 10 to 200 endospores When infected tissues sputum or other discharges are planted on Sabouraud s medium the endospores germinate and grow out as mycelia

Immunology All strains of *C immitis* apparently contain identical antigens During the course of the primary infection the patient exhibits precipitins and complement fixing antibodies and the skin becomes sensitive to coccidioidin The precipitins and complement fixing antibodies disappear after recovery but the skin sensitivity like that to tuberculin is relatively permanent

Pathology In chronic coccidioidomycosis the organisms are surrounded by epithelial cells giant cells lymphocytes and plasma cells Abscess formation is more frequent than in tuberculosis especially in the bones and subcutaneous tissues Abbott and Cutler described three types of meningeal lesions one is practically identical with tuberculous meningitis a second has larger more granulomatous lesions and the third shows a thick accumulation of plastic exudate

Clinical Manifestations In some areas in the southwestern United States positive skin tests with coccidioidin have been found in 50 to 84 per cent of the population indicating that primary infection with *C immitis* is common but usually asymptomatic When the reaction to infection is severe enough to be recognized as a disease the symptoms signs roentgenographic changes and course of the disease parallel that of primary tuberculous infection The patients have malaise anorexia chills fever headache backache night sweats and pleurisy The cough produces a scant amount of mucoid or mucopurulent sputum which contains the characteristic spherules of *C immitis* The organisms have been found in pleural fluid Roentgenograms of the lungs may show thickening of the hilar region peribronchial thickening or patches of nodular or bronchial pneumonitis The larger more solid lesions may break down and leave thin walled cavities which usually heal in a few weeks or months but may persist for years Sensitivity to coccidioidin appears after seven to fourteen days and skin lesions resembling those of erythema nodosum or erythema multiforme develop in 20 per cent between the fifth and fourteenth days of the disease and persist for one to four weeks This form of the disease has been known for years as "valley fever" "desert fever" "San Joaquin fever" or "the bumps" Although recovery is usually rapid and complete an occasional case passes into the progressive virulent type of the disease with involvement of bones subcutaneous tissues and internal organs including the brain

Sometimes the organism gains entrance through the skin or possibly through the tonsils Lesions of the cervical lymph nodes have been described which simulate those of tuberculous adenitis

Diagnosis One should suspect coccidioidomycosis in any obscure disease originating in a native of the endemic area and in persons who have visited such areas *Coccidioides immitis* can be found in the sputum in the primary infection In the progressive type the organisms are present in the sputum in the subcutaneous abscesses and in the lesions of the internal organs In progressive coccidioidomycosis there is a steady increase in the complement fixing antibodies while the skin sensitivity decreases or disappears

Coccidioidomycosis must be differentiated from tuberculosis syphilis glanders bacterial osteomyelitis epithelioma and other mycoses

Prognosis The prognosis is excellent in primary pulmonary involvement good in the dermal and lymph node types of the disease when they are a part of the primary infection but most grave in the generalized and meningitic types

tionized the therapy of blastomycosis Most of the previously incurable systemic infections can be cured and the response of the other types is more rapid than with the older vaccine iodide regimen Stilbamidine is the more toxic of the two drugs Most systemic cases can be cured with maximum daily doses of 225 mg of hydroxystilbamidine a day for thirty days or with alternate periods of ten days of treatment and ten days of rest until the total dose of 8 to 12 gm has been administered The dose of 225 mg should be diluted in 300 ml of physiological saline or in 5 per cent glucose in distilled water and administered intravenously over a three hour period The drug should be protected from daylight both during preparation and during administration to prevent the development of toxic degeneration products

Relapses do occur as long as six months to two years after an apparent cure In most instances the relapses have occurred in patients with necrotic bone lesions or in other areas which are not adequately drained Another course of hydroxystilbamidine should be started and surgical drainage instituted If a second relapse occurs the new fungicidal drug amphotericin (Fungizone [Squibb]) should be tried (see Coccidioidomycosis)

Cutaneous blastomycosis usually responds satisfactorily to local roentgen therapy when given simultaneously with potassium iodide and subsequently to desensitization of the sensitive patient

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Geotrichosis

The bronchi and lungs and occasionally the mouth and intestinal tract may be attacked by one or more species of the genus Geotrichum The oral lesions resemble those of thrush and the pulmonary infection simulates blastomycosis Usually the patient has symptoms of bronchitis or of a rather mild but chronic type of bronchopneumonia In the more severe forms of the disease blood may be present in the sputum and cavities develop in the lungs The Geotrichum is frequently a secondary invader in chronic Klebsiella (Friedländer's bacillus) infection of the lungs and occasionally in tuberculosis

Mycology The organism grows readily on Sabouraud's medium at room temperature and at 37° C There is a budding form of Geotrichum which is readily confused with the budding form of Blastomyces but this budding form is always accompanied by the rectangular conidia which are characteristic of the genus

Treatment The oral lesions respond to the gentian violet treatment described for *Candida albicans* The intestinal form should receive oral doses of gentian violet in salol-coated capsules in doses of 32 mg three times a day The bronchial and pulmonary forms have a good prognosis when treated with an autogenous vaccine and oral potassium iodide Resistant cases should be given a trial with amphotericin (see Coccidioidomycosis)

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Coccidioidomycosis

Definition Primary coccidioidomycosis is an acute infection with a good prognosis but may develop into progressive coccidioidomycosis which is a generalized granulomatous disease with a high mortality

History Posadas and Wernicke recognized the disease in Buenos Aires in 1892 Rixford reported a case from California in 1894 and Rixford and Gilchrist studied a series of cases in 1896 In 1900 Ophuls and Moffitt cultivated the organism and demonstrated that it was a fungus and not a protozoan

Incidence The disease is encountered most frequently in southern California but

throughout the world The organism has been isolated from fruit juices milk from cows with mastitis and from pigeon manure

Mycology *Cryptococcus neoformans* grows readily on Sabouraud s medium the initial colonies appearing after four to twelve days incubation at 37° C The colonies are medium in size soft mucoid with a creamy color On examination the oval or slightly elongated cells 5 to 6 μ in diameter are surrounded by large capsules which are outlined clearly in India ink preparations This fungus multiplies by budding it does not form ascospores or mycelium There are several immunological types as determined by capsular swelling with specific serums

Immunology Patients usually exhibit no precipitins agglutinins or complement fixing antibodies but filtrates from cultures have given positive skin tests of the delayed type

Pathology Mook and Moore described acneiform pustules granuloma like ulcers deep-seated abscesses and nodules which may increase in size and simulate "myxomatous tumors" Giant cells and foam" cells are numerous fibroblasts lymphocytes and plasma cells are present but there is a remarkable paucity of polymorphonuclear leukocytes In several instances the tissue reaction was similar to that seen in Hodgkin s disease The encapsulated organisms are present both in and outside of giant cells but there is an almost complete *absence of leukocytes*

Clinical Manifestations The patient may present single isolated abscesses subcutaneous tumor like masses or multiple subcutaneous abscesses as in the original case *of Busse and Buschke The primary pulmo*nary lesions resemble those of primary carcinoma or reinfection tuberculosis

In the more common cerebral type of infection the onset is insidious with headache dizziness vertigo and stiffness of the neck Occasionally the onset is sudden with violent and excruciating headache and vomiting The patient has little or no fever and the pulse and blood pressure remain normal The disease often is mistaken for a rather chronic type of tuberculous meningitis After several weeks or months more severe symptoms and signs appear such as neuroretinitis papilledema strabismus nystagmus ptosis diplopia ataxia or hemiplegia The patient ultimately becomes comatose and dies of respiratory failure

Diagnosis The dermal subcutaneous and lymph node lesions may be diagnosed by routine biopsies and cultures on Sabouraud s medium The diagnosis of the pulmonary forms is made by growing the organism from the sputum In the meningeal form of the disease the cerebrospinal fluid pressure is increased and the fluid usually contains 200 to 800 cells per cu mm which are chiefly mononuclear The cerebrospinal fluid sugar is decreased The cryptococci are present in small numbers and are readily mistaken for erythrocytes or lymphocytes After centrifugalization the sediment from the fluid should be planted on Sabouraud s medium and watched for three or four weeks Not infrequently the organism can be found by direct examination if a drop of the sedimented material is mixed with India ink

Prognosis The prognosis is grave in all forms of the disease especially the cerebral form which until recently has been considered inevitably fatal

Treatment A number of patients have been treated with the new fungicidal drug amphotericin (see Coccidioidomycosis) Except in moribund cases the immediate results have been dramatic following the intravenous administration of this antimicrobial Some patients have remained well for as long as two years

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Histoplasmosis

Definition Histoplasmosis resembles coccidioidomycosis in having a benign primary pulmonary phase and a less common severe generalized form which involves the reticuloendothelial system

History In 1906 Darling in Panama found round or oval parasites *which he thought were protozoa* in the endothelial cells and monocytes of certain cases of splenomegaly Dodd Tompkins and De Monbreun in 1934 isolated *Histoplasma capsulatum* from a typical clinical case in a child and discovered that the parasite was a *fungus*

Treatment Most primary pulmonary infections heal rapidly in a few weeks without *specific treatment* The primary cases which have persistent thin walled cavities present a difficult problem If symptoms persist for more than six months the infected area should be removed by segmental lobectomy

The *generalized and meningeal infections* are very difficult to treat however the new fungicidal drug amphotericin offers some hope for these unfortunate patients Amphotericin is available in two forms one for intravenous *and one for oral* therapy The initial dose of the intravenous preparation is 0 25 mg per kg of body weight and the dose is increased by 0 25 mg every two or three days up to 1 0 mg per kg The drug is dissolved in 1 0 liter of sterile 5 per cent glucose in distilled water and administered by intravenous drip over a six hour period Heparin may be added to reduce thrombosis of veins Acetyl salicylic acid and antihistaminics should be administered at the beginning of the injection to minimize the slight febrile reactions which sometimes accomany or follow the injections The treatment should continue for at least thirty days and sometimes for two to three months

The oral *treatment* has *not* been *stand*ardized The dose will vary with the purity of the preparation All seriously ill patients should have the intravenous injections initially

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South American Blastomycosis

South American blastomycosis is a chronic granulomatous disease quite similar in its clinical course to coccidioidomycosis

At present the disease is confined to South America where De Almeida has collected the reports of 255 cases The portal of entry is frequently in the area about the mouth and there is ulceration of the intestinal tract and adenopathy severe enough to suggest Hodgkin s disease

The organism is found in the tissues as a large (10 to 30 μ) round doubly contoured form with multiple small buds about the periphery which were originally mistaken for endospores It grows readily on Sabouraud s *medium* and on *blood* agar Conant found that the method of growth and budding on blood agar was more like that of *Blastomyces dermatitidis* than of *Coccidioides immitis*

The disease is usually fatal

Sulfadiazine in daily doses of 2 to 4 gm results in dramatic temporary improvement Amphotericin should be given a trial in this disease (see Coccidioidomycosis)

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Cryptococcosis

(Torulosis)

Definition Cryptococcosis is a subacute or chronic highly fatal infection which may involve any part of the body but has a marked predilection for the brain *and* meninges

History In 1894 Busse and Buschke isolated from a fatal case with multiple lesions of skin and viscera a yeastlike organism which they called *Saccharomyces* but which has now been definitely identified as *Cryptococcus neoformans (Torula histolytica) This disease is called* blastomycosis in the European literature and European blastomycosis" in America to distinguish it from American blastomycosis or Gilchrist s disease which is caused by *Blastomyces dermatitidis*

Etiology Cryptococcosis occurs in all parts of this country and in scattered areas

Candidiasis

Definition Candida may produce acute or subacute infections of the mouth vagina skin nails bronchi and lungs and occasionally a septicemia endocarditis or meningitis

History The organism now known as *Candida albicans* was discovered in oral thrush by Langenbeck in 1839

Etiology The disease is found in all parts of the world at all ages in all races and in both sexes Oral thrush is most common in infants and in patients with wasting diseases Pregnancy and diabetes predispose to vaginal candidiasis Dermal lesions occur in bakers waiters fruit packers bartenders and housewives whose hands are macerated from frequent soaking in water Poorly fitting artificial teeth predispose to infections of the tongue and mouth

Benham isolated both pathogenic and nonpathogenic strains of Candida from normal skin and showed by animal experiments that *C albicans* is the only pathogenic species

Mycology Candida grow readily on Sabouraud's medium after two to four days incubation at room or incubator temperatures The colonies are soft moist oval white structures which have a distinct yeastlike odor *Candida albicans* is lethal for rabbits ferments certain sugars agglutinates in specific serums and forms typical chlamydospores on corn meal agar

Immunology Many normal persons have agglutinins in their blood and a positive skin reaction while some patients with active infection have neither

Pathology Both budding cells and mycelial threads may be found in sputum and in scrapings from the dermal and mucosal lesions

Clinical Manifestations Candida may produce *thrush vaginal candidiasis paronychia onychia intertriginous candidiasis dyshydrosiform eruptions generalized eruptions* and *chronic glossitis* Certain of these entities notably thrush and glossitis may be encountered in chronically ill patients who have been receiving prolonged antimicrobial therapy The precise relationship of the chemotherapy to the furtherance of the Candida infection in such situations has not been established

Bronchitis both the acute and chronic varieties results from bronchial infections The symptoms resemble those of bacterial bronchitis but the sputum usually is mucoid or gelatinous

Pneumonitis occurs as an acute or subacute process The lungs may show massive patchy consolidation in one or more lobes There is cough malaise fever and leukocytosis but usually the patients are less toxic than with bacterial infections The sputum is mucoid or mucopurulent and may contain blood

Diagnosis The diagnosis is established by cultivating and identifying the potentially pathogenic *Candida (Monilia) albicans* Candida is frequently a secondary invader in tuberculosis pulmonary abscess bronchiectasis neoplasm and even other types of mycoses

Prognosis The pulmonary and septicemic forms may be fatal The bronchial and localized infections are often chronic and resist treatment but rarely kill the patient

Treatment Bronchial and pulmonary moniliasis should be treated with potassium iodide In some cases the patients have positive skin tests to Candida vaccines and may not respond to the iodides until partial desensitization with vaccine has been effected The severe chronic generalized infections of skin nails and intestines in children have resisted all known forms of therapy The new fungicidal drug amphotericin should be tried in these cases since the fungus is suceptible to this drug in the test tube

The acute oral lesions usually respond to alkaline washes or to gargles with 1 10 000 gentian violet Recently a jellylike preparation of sodium propionate has been found very effective in curing Candida vaginitis

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Sporotrichosis

Definition Sporotrichosis is a chronic infection characterized by the formation of gumma like nodules abscesses and ulcers The lesions usually are confined to the skin and superficial lymph nodes

Etiology Histoplasmosis occurs throughout the world and in all parts of the United States but appears in greatest concentration in the Central Mississippi and the Ohio River valleys All races are susceptible and both sexes are attacked at all ages but adult males seven times as frequently as females Children seem to be relatively more susceptible than to other mycotic infections and male and female children are infected in equal numbers Spontaneous histoplasmosis has been found in dogs rats mice and skunks The organisms grow in profusion in pigeon bat and chicken dung and the inhalation of these dried materials has given rise to epidemics of histoplasmosis

Mycology The organism can be isolated directly from the blood sputum sternal bone marrow or from tissues at necropsy by planting the material in dextrose agar or dextrose broth at 37° C Two types of colonies appear one of them a mycelial type and the other a yeastlike type

Pathology Primary pulmonary histoplasmosis appears as multiple small discrete spots in the lungs with associated infection and enlargement of the tracheobronchial lymph nodes As healing occurs the organism disappears and the central portions of the lesions become caseous and later calcify In rare instances as shown by Dublin the primary infection behaves like a primary progressive tuberculosis and kills the patient Johnson has found several cases which showed the multiple calcification that is characteristic of healed primary infections in which reinfections have occurred with the development of cavities and of pulmonary fibrosis

Histoplasma capsulatum is an intracellular parasite which in progressive cases invades the entire reticuloendothelial system

Clinical Manifestations The benign primary pulmonary infections are usually asymptomatic Infections beginning in the mouth larynx pharynx and ears show local necrotic ulcerations and definite enlargement of the regional lymph nodes The progressive form of the disease is characterized by splenomegaly hepatomegaly emaciation irregular pyrexia leukopenia and anemia Not all patients present this complete syndrome the liver and spleen may not be enlarged the disease may be confined chiefly to the lungs or even to the skin as in the case studied by Hansmann and Schenken

Diagnosis The disease should be suspected in every obscure infection in which there is enlargement of the lymph nodes with or without accompanying enlargement of the liver and spleen In most instances within a few weeks after the initial infection the patient has a tuberculin like allergy which can be demonstrated by the intracutaneous injection of 0 1 ml of a 1 1000 dilution of a standardized histoplasmin The reaction is read after forty eight to seventy two hours in the same way as a tuberculin reaction and has a similar significance Most rapidly progressive cases never develop a histoplasmin reaction and terminal cases which formerly reacted may become anergic

Complement fixing antibodies appear in the serum of patients with progressive infections and increase in titer as the disease progresses

Histoplasma capsulatum shares a small amount of common antigen with *Blastomyces dermatitidis* resulting in cross reactions both to the skin tests and to the complement fixation However no confusion will arise if both tests are performed simultaneously C E Smith has found cross reactions to histoplasmin in patients with *Coccidioides immitis* infections although the reactions were always less in extent than to coccidioidin

Prognosis The prognosis is excellent with the primary pulmonary forms dubious in the localized infections and almost hopeless when the infection is generalized

Treatment The new fungicidal drug amphotericin shows great promise as a therapeutic agent in histoplasmosis (*see* Coccidioidomycosis) Several patients with acute generalized infections and one with meningitis improved rapidly after treatment The chronic reinfection type of disease improves slowly but progressively Some patients as in tuberculosis will require resectional surgery

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Maduromycosis

(*Madura Foot*)

Maduromycosis or mycetoma is a chronic infection affecting principally the foot but in rare instances other parts of the body It is characterized by multiple abscesses and sinuses and the development of granulation and connective tissues

Mycology Carter in 1860 proved that the disease was a mycosis and introduced the term "mycetoma or fungous tumor The disease may be caused by any one of thirteen species of the genus Nocardia or any one of nineteen species of molds belonging to two classes and eight genera (Gammel)

Etiology The specific cause is contained in the white yellow deep brown or black granules which appear in the discharges from the affected region The disease is most common in males and in farmers or other persons who come directly in contact with the soil

Pathology The pathological reaction is essentially the same regardless of the type of invading fungus There is local and general swelling of the parts affected with a corresponding degree of deformity In old chronic cases the skin is darkened and the surface studded with pitted scars open sinuses and nodular fungating elevations Dense masses of scar tissue are found in the healing lesions The abscesses connected with the sinuses are filled with mucoid fluid in which the characteristic granules are floating

Prognosis and Treatment Sulfonamide therapy may cure the type of maduromycosis which is caused by Actinomyces or Nocardia The disease does not heal spontaneously and the patients eventually die of secondary infection unless the infected limb is amputated

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Chromoblastomycosis

Chromoblastomycosis or verrucous dermatitis is characterized by the formation of warty cutaneous nodules which through slow progressive growth become transformed into prominent papillomatous vegetations which may or may not ulcerate Usually the lesions are confined to the feet and legs but may be limited to the hands and arms In 1911 Pedroso of Sao Paulo Brazil isolated a pigmented organism from patients with verrucous lesions of the skin which was later named *Hormodendrum pedrosoi* Large spherical bodies dark brown in color are present in abundance in the verrucous lesions and grow readily on Sabouraud s medium

Pathology The disease is chronic and may last for years With the development of extensive fibrosis in the deeper dermal lesions the lymphatics are blocked and the patient suffers an elephantiasis of the extremity

Treatment Complete destruction of the lesion by surgical excision or electrotherapeutic methods would seem to be logical when the disease is diagnosed in its incipient stage Surgical amputation is not justifiable because the lesions rarely become severely infected and usually make sufficient response to medical tratment to leave the patient with a useful limb The internal treatment consists of large doses of potassium iodide up to as much as 1 0 to 9 0 gm per day Iontophoresis with copper sulfate was used with considerable success in the case reported by Martin Baker and Conant

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History Schenck in 1896 isolated a fungus later identified as Sporotrichum by E F Smith from a patient in Johns Hopkins Hospital The second case was described by Hektoen and Perkins in 1900 who named the fungus *Sporotrichum schenckii* The disease was recognized in France in 1903 by de Beurmann and Raymond and their organism was named *Sporotrichum beurmanni* by Matruchot and Raymond

Etiology The disease occurs throughout the world but most often in males especially farmers laborers and horticulturists The primary lesion was on some part of the upper extremities in 90 of 102 cases Sporotrichosis occurs spontaneously in horses dogs and rats Meyer infected himself while working with an equine strain Plants may be the primary host

Mycology The yeastlike tissue form of the organisms will grow on Francis glucose cystine blood agar at 37° C in five to ten days The white moldlike form grows on Sabouraud s medium at room or incubator temperature after five to ten days and slowly becomes brown or black on further incubation

Immunology Agglutinins and complement fixing antibodies may appear in the serum and occasionally a tuberculin like sensitivity develops in the patient

Pathology The gumma like nodules usually consist of a central abscess surrounded by granulation tissue with giant and epithelioid cells and a peripheral zone of connective tissue histologically resembling syphilitic tuberculous or other chronic inflammations In the living tissue Sporotrichum occurs as oval bodies of fairly uniform size 2 to 3 μ broad and 3 to 5 μ long

Clinical Manifestations The primary lesion usually is in the skin and may appear as early as twenty days or as long as three months after the initial infection The primary lesion is a hard spherical elastic movable subcutaneous nodule not adherent to the overlying skin It becomes attached to the skin which first becomes pink and then purplish and finally black and necrotic This lesion (sporothrix chancre) may persist for months Usually after a few days or weeks multiple subcutaneous nodules appear along the course of the lymphatic drainage These nodules are at first freely movable but later adhere to the overlying skin become reddened and ulcerate through to the surface discharging a small amount of thin pus The lymph vessels between the nodes may become so thickened they can be felt as hard cords

De Beurmann and Gougerot classified the clinical types of the disease as (1) lymphatic (2) disseminated (3) epidermal (4) sporotrichosis of the mucous membranes (5) skeletal sporotrichosis and (6) visceral sporotrichosis In the rare disseminated gummatous form single or successive crops of nodes develop at intervals Pulmonary sporotrichosis with cavitary lesions in the lungs is being found with greater frequency

Diagnosis The diagnosis is established by cultivating the organisms from the discharges or from material removed at biopsy The disease may simulate syphilis tuberculosis blastomycosis cryptococcosis glanders tularemia leprosy or pyogenic infections

Prognosis Uncomplicated sporotrichosis is rarely fatal when untreated it persists for months or years but appropriate treatment usually is followed by healing

Treatment Potassium iodide should be given in slowly increasing doses up to 4 to 6 gm or more daily If absorption of closed abscesses is slow they may be punctured aspirated and injected with a weak solution of iodide Incision and curettage are to be avoided Ulcerated lesions may be painted with tincture of iodine and dressed with a solution containing water 500 ml potassium iodide 10 gm and iodine 1 0 gm The treatment should be continued for at least a month after apparent recovery Some of the generalized visceral infections respond incompletely to potassium iodide therapy These should be treated with hydroxystilbamidine (see Blastomycosis) or amphotericin (see Coccidioidomycosis)

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infection in a lobe of the lung intestine or sinus should be considered when feasible

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Rhinosporidiosis

Rhinosporidiosis caused by *Rhinosporidium seeberi* is characterized by the development of pedunculated or sessile polyps in the nose and conjunctivas The disease is prevalent in India and Ceylon but occurs in temperate regions More than fifteen cases have been recognized in the United States

The diagnosis is established by demonstrating the sporangia and spores in the tumor tissue Surgical excision cures the early cases

DAVID T SMITH

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Aspergillosis

Certain species of Aspergillus especially *Aspergillus fumigatus* produce inflammatory granulomatous lesions in the skin external ear vagina nasal sinuses orbit bronchi lungs and occasionally bones and meninges The disease was first recognized by Bennett in 1842 and the first careful necropsy of pulmonary aspergillosis in man was by Virchow in 1856 Renon s monograph published in 1897 established the frequency and importance of aspergillosis in France

Extensive pulmonary lesions may occur in instances in which there are overwhelming exposures to the spores as in pigeon feeders hair cleaners and certain agricultural workers Two chronic forms of pulmonary aspergillosis can be recognized The first appears as a migrating pneumonitis of the allergic type and the second results in the development of dense round sharply circumscribed balls which vary in diameter from 5 mm to 5 cm and in number from one to ten or more Aspergilli grow readily on dextrose agar or Sabouraud s medium at either room temperature or at 37 C Infection may be suspected from the greenish or brown color of the discharges Aspergilli are frequently secondary invaders or accidental contaminants and the diagnosis should not be made exclusively on the appearance of the organism on culture One should demonstrate the mycelial forms directly in the discharges before the material is planted

The standard treatment is with potassium iodide If hypersensitiveness to an autogenous Aspergillus vaccines can be demonstrated then vaccine therapy is also indicated The migrating allergic type of aspergillosis frequently improves following the administration of autogenous vaccines made from the fungus and from all bacteria isolated from the sputum to which the patient gives a positive skin test The solid ball like lesions shoud be removed surgically by wedge resections

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Penicilliosis

Several species of the genus Penicillium are capable of producing lesions in the ear and skin and occasionally in the lungs Clinically the infections resemble those caused by the Aspergillus and the same care has to be exercised in establishing the etiological relationship between the culture and the disease The treatment is the same as for aspergillosis

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Mucormycosis

The first authentic case of mucormycosis in man was reported by Paltauf in 1885 The disease is being recognized with increased frequency at the present time

Mucormycosis may be caused by any one of the three genera Mucor Absidia or Rhizopus which make up the order Mucorales The infection occurs most often in patients with uncontrolled diabetes leukemia or myeloma and in patients treated with corticosteroid hormones or broad spectrum antimicrobial drugs

The infection begins most often in the orbit or sinuses but may start in the lungs or intestines The organisms grow in the walls of the blood vessels and cause death by metastases to the brain and other vital organs

The treatment is directed to restoring the patient s resistance to normal by controlling the diabetes and removing the deleterious hormones or clinical agents Theoretically immunity might be increased with heat killed vaccines made from the patient s own organism as employed by Harris in the first clinical cure of mucormycosis Surgical excision of the focus of

fection has become sufficiently intense to result in metastatic lesions in the skin and mucosa

Less precise knowledge is available concerning the length of time during which detectable reagin will persist in the serum of persons who receive no treatment It is probable that the serological tests for syphilis once positive do not spontaneously revert to negative for at least ten years Whether spontaneous serological reversal occurs in a significant number of patients (exclusive of tabetics) after the first decade of the disease has not been established but this probably occurs in some persons

The antibody detected by the treponemal immobilization test once present apparently persists for life The appearance of this antibody can be prevented however by appropriate treatment very early in the course of syphilitic infection

CLINICAL PICTURE OF SYPHILIS

Acquired Syphilis of Adults *Early Syphilis (Infectious or Early Latent)* Infectious syphilis is the generalized form of the disease in which one or more lesions rich in *T pallidum* are present on the exterior of the body The lesions may appear at any time from a week to several years after onset of infection In an appreciable number of instances (females 50 per cent males 30 per cent) the lesions either fail to appear at any time or remain unrecognized by the infected person Infectious lesions vary in character and extent from a solitary primary or metastatic lesion to a generalized involvement of the skin and mucous membranes The initial or primary lesion serves as an historic landmark of the portal of entry of the infection but is otherwise intrinsically the same as the metastatic lesions Even the value of the primary lesion as a landmark is modified by the fact that solitary metastatic lesions occur and may be erroneously identified as primary *Frequently when the patient is* first observed by the physician both primary and metastatic lesions are present

SYMPTOMS OF INFECTIOUS SYPHILIS A unique feature of the early syphilitic infection is the fact that it usually produces virtually no symptoms of systemic disease despite the presence of spirochetemia and widespread metastatic lesions A possible exception is headache which may occur as a manifestation of the generalization of the infection but more often is a reflection of metastatic involvement of the central nervous system or skull Fever occurs only rarely and seldom rises higher than 100 2° F (38° C) The urine is normal There is no anemia or leukocytosis of the peripheral blood

Because of the virtual absence of systemic symptoms the patient with syphilis may not seek medical care during the period of infectiousness unless local lesions give rise to symptoms or awaken a suspicion of disease Thus the physician is usually faced with the problem of identifying a serious generalized infection from a clinical manifestation which appears to be purely local and trivial in nature

The *initial lesion* (primary chancre) may appear at any time between the tenth and the ninetieth day after infection but usually is evident within two or three weeks *There is nothing fundamentally characteristic about the appearance of a chancre* The diagnosis can be established only by the demonstration of the presence of the organisms in the lesion even though the syphilitic etiology may be suspected from clinical examination Because of the subacute nature of the inflammatory process with the extensive occlusion of small vessels the chancre tends to be indurated circumscribed relatively avascular and painless Any or all of these characteristics may be so modified by the location of the lesion and the presence of other infectious processes that no typical picture is consistently produced

As would be anticipated from the epidemiology of syphilis the initial lesion usually occurs on the skin or mucous membranes of the genitalia the perianal region the lips or the oral cavity Less frequently the finger or the female breast is the site of implantation of the organisms An ulcerative lesion of these or other areas particularly one which persists for several weeks may represent the initial lesion of syphilis and can be identified as such only by the proper use and interpretation of laboratory *examinations*

Regardless of the site of infection the appearance of the chancre is usually accompanied by a moderate enlargement of the regional lymph nodes The nodes are firm discrete movable and are not usually tender Syphilitic infection does not lead to suppuration of lymph nodes but occasionally a purulent process may develop in inguinal nodes which are involved simultaneously by syphilis and another infection

On the genitalia multiple infectious lesions of syphilis are common particularly in the female In the latter instance the

found convenient therefore to subdivide the term *latent syphilis* into early or late at a point four years after the onset of infection The line of division is arbitrary and is based on the assumption true in virtually all instances that after four years the reappearance of the generalized stage of the infection is no longer to be anticipated

Early latent syphilis thus may return to the metastatic or infectious variety Once the focalization of the process becomes stabilized the disease enters into the stage either of *asymptomatic neurosyphilis* or of *late latent syphilis*

Late Latent Syphilis After the stage of late latency has been reached the infection may pursue any one of three possible courses (1) The foci still present after resolution of the infectious lesions may heal slowly over a period of years with complete eradication of the infecting organisms (biological cure) The incidence of this phenomenon is not known but it probably occurs in approximately 25 per cent of those infected (2) The foci of infection may persist throughout the life of the host but evoke such a minimal or fortuitously located tissue reaction that the health of the infected person is unimpaired This course which is analogous to the healthy carrier state in other infections undoubtedly occurs with frequency (3) The foci may progress at a slow and inconstant rate until sufficient tissue reaction has occurred to produce clinical evidences of disease This occurs in approximately 15 per cent of the persons with late latent syphilis The resulting clinical disease may be fatal or benign depending upon the amount of damage and the importance of the structure affected Although there is virtually no prospect that a person with late latent syphilis (cerebrospinal fluid normal) will subsequently develop neurosyphilis the person with neurosyphilis may eventually develop clinically demonstrable lesions in other areas of the body in the same manner as occurs in late latent syphilis

Location and Character of the Lesions of Late Syphilis Syphilis may attack virtually any organ or tissue of the body In the past this fact has been grossly overemphasized for almost without exception serious or fatal syphilis in adults is limited to involvement of the aorta the central nervous system or the eye Less frequently the infection becomes evident as the localized single or multiple granulomas which are designated as gummas The fundamental histopathological lesion of the late forms of syphilis is essentially the same as that of the early lesions and consists of vascular and perivascular cellular infiltration associated with tissue necrosis and ultimate fibrosis The chief features which distinguish early from late lesions are that in the latter the amount of necrosis is greater and the cellular reaction less intense Moreover the treponemes are present in the late lesions only in small numbers and are difficult to demonstrate Gummas increase in size at an inconstant rate and the destruction of tissue is accompanied by partial healing and fibrosis

Prenatal Syphilis The lesions of prenatal syphilis resemble in general the lesions of acquired syphilis of comparable duration However in infants who fail to survive for more than a few weeks (or in stillborn infants) the syphilitic process is unusually acute and is characterized by massive spirochetal invasion of all tissues including the lung (*pneumonia alba*) Aortic syphilis which is so common in the infection acquired by adults occurs only rarely in those who survive a prenatal infection

Serological Response to Syphilitic Infection Shortly after infection with *T pallidum* two distinct antibodies become detectable in the serum of the host One of these designated *syphilis reagin* exists in close association with the gamma globulin fraction of the plasma the other known as *treponemal immobilizing antibody* (T P I) can be detected by an *in vitro* test originated by Nelson

Only the first named antibody *syphilis reagin* can be detected by the various serological tests for syphilis (hereinafter designated S T S) As with serological tests in other infections the amount of syphilis reagin present in a specimen of serum can be crudely quantitated by repetition of the test with serial dilutions of the unknown serum The highest dilution of serum which contains detectable reagin is designated as the titer of the reaction

The interval between the onset of infection and the appearance of detectable reagin in the serum is dependent upon the sensitivity of the technique employed and varies among individual infections Usually the S T S becomes positive between the third and the sixth weeks after the disease has been contracted In a minority of instances however the process requires more time and the serological tests may not become positive until approximately three months after the onset of infection With modern techniques the S T S is invariably positive when the dissemination of the in

fection has become sufficiently intense to result in metastatic lesions in the skin and mucosa

Less precise knowledge is available con cerning the length of time during which detectable reagin will persist in the serum of persons who receive no treatment It is probable that the serological tests for syph ilis once positive do not spontaneously revert to negative for at least ten years Whether spontaneous serological reversal occurs in a significant number of patients (exclusive of tabetics) after the first decade of the disease has not been established but this probably occurs in some persons

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On the genitalia multiple infectious le sions of syphilis are common particularly *in the female In the latter instance the*



FIG 37 Infectious syphilis metastatic cutaneous lesions



FIG 38 Late syphilis cutaneous gumma of elbow before treatment

lesions are usually metastatic In the male multiple chancres of the penis are by no means rare

The primary lesion of syphilis is frequently but by no means invariably accompanied or followed by the development of metastatic lesions of the skin and mucous membranes Regardless of whether secondary lesions occur the initial lesion slowly heals usually in a two to six week period and may or may not leave a thin atrophic scar The regional lymphadenopathy subsides less rapidly and may be present in some degree for several or more months The generalized enlargement of the lymph nodes may resolve or may persist and become more prominent if widespread metastatic lesions develop

Metastatic Lesions (Secondary Syphilis) The visible manifestations of the generalization of the syphilitic infection are encountered chiefly in the skin and mucous membranes The surface involvement varies in extent from one or several lesions in a single area to widespread involvement of skin and mucosa Although the cutaneous and mucosal lesions frequently coexist it is important to realize that they may occur independently of each other The character of the cutaneous lesions is protean With the exception of a vesicular eruption which is never produced by acquired syphilis virtually any type of rash may develop The forms which are most frequently encountered are a faint red macule (1 to 3 mm in diameter) a reddish brown papule or a folliculopapule Although the pigmentation of the papule is presumably caused by the extravasation of blood the process never becomes sufficiently acute to give rise to hemorrhagic lesions Less frequently the infection produces an annulo papular pustular rupial (ulcerated) or psoriasiform eruption The annulopapular pustular and folliculopapular varieties are encountered more frequently in Negroes

The distribution of the cutaneous lesions may be of more value than the morphology in directing the suspicion of the clinician toward the possibility of the presence of syphilis As the infection is blood borne the lesions are generalized and may develop on the palms soles and face in addition to or independently of involvement of the skin of the trunk and extremities In infections other than syphilis (meningococcemia staphylococcemia the rickettsial and viral diseases) in which skin lesions appear in the characteristic blood borne distribution the patient usually presents obvious evidence of acute systemic disease Syphilitic lesions of the palms or soles usually appear as dark reddish brown macules or papules Occasionally on the hands and feet the infection may produce a superficial scaling eruption which simulates a fungal infection

INVOLVEMENT OF MUCOUS MEMBRANES Metastatic (secondary) syphilitic involvement of the mucous membranes may ap

pear as a simple erosion a papulo-erosion or as a hypertrophic papular or symmetrically spread lesion which is designated by the term *condyloma latum* * The simple erosive and papulo erosive lesions occur in the buccal mucosa or on the genitalia The erosion is usually covered by a thin silvery gray membrane (*mucous patch*) and is surrounded by little inflammatory reaction Multiple lesions are common particularly in the oral cavity The erosions do not usually produce any symptoms unless they are located on the tonsillar pillar or tonsil where they may cause moderately severe symptoms of a tonsillitis or pharyngitis

Condyloma latum occurs most frequently in moist areas such as the lips the female genitalia and in the perianal region of both sexes On the labia majora the lesions are usually multiple and consist of flat raised nodules which are approximately a centimeter in diameter In the other areas particularly around the anal orifice the condyloma may appear as an indurated slightly raised purple brown lesion which extends symmetrically over the surrounding skin for an area of 2 or 3 cm Unless traumatized or secondarily infected condylomas are not usually ulcerated A perianal condyloma like any lesion close to the anal sphincter may cause considerable pain on defecation In the presence of this symptom the highly infectious condyloma is frequently mistakenly identified as a "fissure or a "thrombosed hemorrhoid"

A mucocutaneous lesion of syphilis which is deserving of special mention is the so called "*split papule*" The lesion consists of a tiny moist papule which develops at the angle of the mouth where it becomes split in one or more places A papule in this location may represent the sole demonstrable lesion of a syphilitic infection yet may easily be overlooked because of the frequent occurences of innocuous traumatic fissures at the corners of the mouth

INFECTIVITY OF CUTANEOUS AND MUCOSAL LESIONS All of the cutaneous and mucosal lesions of early syphilis contain *T pallidum* in considerable numbers and hence are potentially infectious for others The most dangerous lesions from the standpoint of transmissibility are the innocuous appearing ulcerated lesions about the lips or in the mouth

EARLY NEUROSYPHILIS Involvement of the central nervous system during the course of infectious syphilis is demonstrable in an appreciable number of patients by examination of the cerebrospinal fluid Usually this inflammatory process is not sufficiently intense to produce symptoms other than a mild or moderately severe headache Occasionally however the presence of the infection in the central nervous system becomes clinically evident *This early symptomatic neurosyphilis is an extremely rare occurrence among patients with untreated infectious syphilis but develops not infrequently in patients who have received subcurative therapy* The presenting clinical picture of early symptomatic neurosyphilis is characterized by evidence of disease of the meninges or of the arteries of the brain and is discussed in a subsequent chapter

OTHER METASTATIC LESIONS OF EARLY SYPHILIS The metastatic lesions of early syphilis which may occur in addition to those already described are a generalized enlargement of lymph nodes only rarely accompanied by splenic enlargement alopecia of an irregular moth-eaten type distinct from the completely hairless areas of alopecia areata and three types of ocular disease *iritis neuritis* or *retinitis* For a detailed presentation of the ocular involvements which may occur during the course of infectious syphilis the authoritative review of Woods should be consulted

It is reasonable to assume that the development of metastatic lesions during the course of infectious syphilis is not limited to those structures in which the presence of infection is so easily demonstrated Nevertheless the development of clinically detectable disease of other organs or structures is remarkably infrequent

Diagnosis of Infectious Syphilis No matter how experienced the clinician or how characteristic the lesions the diagnosis of infectious syphilis cannot be established with certainty except by darkfield microscopy Less certain but generally acceptable evidence of the presence of the infectious state is the finding of consistently positive S T S in a patient who presents lesions which have the appearance of syphilis and which respond promptly to antisyphilitic therapy Although patients who present this combination of findings are usually syphilitic there is no proof that the infection is recent and the presumed infectious lesions may represent manifestations of a coincidental disease Despite the fact that the proof of the diagnosis of infectious syphilis rests entirely on laboratory procedures it is essential that the physician be alert for possible clinical evidences of syph

* Not to be confused with *condyloma acuminatum* the venereal or genital wart which has the characteristic appearance of warts occurring elsewhere

ilis in order that the laboratory tests may be properly employed

The finding of a genital lesion no matter how nondescript or apparently benign should immediately arouse a suspicion of syphilis The possibility of syphilis should also be suggested by the presence of a lesion particularly one which persists for several weeks anywhere on the body Moreover a cutaneous eruption of blood borne distribution in a patient who shows no evidence of acute systemic infection is *highly suggestive of infectious syphilis In* the presence of these frank manifestations of syphilitic infection the physician is usually prompt in obtaining the necessary diagnostic laboratory tests In an impressive number of instances however the presence of syphilis is by no means so readily apparent The greatest opportunity for error does not arise from the presence of a genital lesion or a generalized eruption but from the apparently solitary lesions in other areas The tendency is strong for the physician or the regional specialist to regard a particular abnormality as a *localized and trivial disease and to fail to* ascertain that similar abnormalities are present in other regions of the body

Exclusion of the Presence of Infectious Syphilis Not infrequently the physician is confronted by a patient who fears that he has contracted syphilis from a particular exposure and who presents cutaneous or mucosal lesions genital or otherwise in which *T pallidum* cannot be found The question immediately arises as to whether the eruption or ulceration is a manifestation of infectious syphilis In the case of a generalized cutaneous eruption the problem may be solved immediately by the performance of an S T S If the test is negative syphilis can be excluded from consideration for the serological tests attain virtually 100 per cent sensitivity in the presence of a generalized eruption The problem is not so easily solved if the lesion is solitary The proper procedure is to examine material from the suspected lesion under the darkfield microscope for three successive days and to obtain blood for serological testing If no spirochetes are found and the lesion heals S T S should be obtained at four or five day intervals during the first two weeks and at two week intervals thereafter The serological follow up should be continued for ninety days after the suspected exposure or after the appearance of the lesion if multiple exposures had previously occurred The physician should emphasize the fact that the negative S T S obtained during the course of the period of observation do not exclude the presence of early syphilis To be sure as the follow up continues from week to week the significance of negative tests is steadily increased and the chances that the person is developing syphilis become increasingly *remote*

Early Latent Syphilis The term *early latent syphilis* merely designates those patients who fail to present any lesions of infectious syphilis at the time of examination As mentioned previously the patients with early latent and with overt infectious syphilis present essentially the same problem in management The diagnosis of early latent syphilis is made from (*a*) a history of a recent diagnosis of infectious syphilis (*b*) serological evidence of syphilis in a person with a history suggestive of a recently acquired infection (*c*) discovery of serological evidence of syphilis in a person known to have been free from infection in the recent past

LATE SYPHILIS

Late Latent Syphilis An understanding of the clinical entity of *late latent syphilis* is essential for approximately 80 per cent of the syphilitic patients seen by the practitioner are in this stage of the disease Many patients with late latent *syphilis are either* grossly overtreated or sadly neglected Once true latency has been established the subsequent course of the infection is usually benign It is important therefore that this relatively benign and frequently *encountered* form of syphilis be clearly distinguished from the potentially serious types of infection which may *require different* therapy

As defined previously *late latent syphilis* is the term which designates those patients with serological or historical evidence of syphilis of more than four years duration but in whom no evidence of syphilitic disease is detectable by (*a*) complete physical and neurological examination (*b*) an examination of the cerebrospinal fluid (*c*) roentgenographic examination of the heart and aorta

Unless these criteria are met it is possible to overlook detectable and potentially serious syphilitic infection Therefore the physician should obtain the information made available by these three procedures as quickly as possible Although the problem of establishing the latency of a syphilitic infection presents no difficulties it may be difficult to prove that the infection is of more than four years in duration Fre

quently the patient will relate a history of the previous discovery of a positive sero logical test or of some lesion which was diagnosed and treated as syphilis In the absence of such a history the physician must exercise his own judgment as to whether the undoubtedly latent infection is recent or old As with other chronic infec tions such as tuberculosis it is advisable to regard syphilis of unknown duration in a young person as a recently acquired in fection

Syphilis of the Cardiovascular and Cen tral Nervous Systems Virtually all of the fatalities from syphilis arise from involve ment of either the cardiovascular or central nervous systems It is not generally appre ciated that aortic and neurosyphilis fre quently occur together These two most serious forms of syphilis are discussed in following chapters

Ocular Involvement in Late Syphilis The most frequently encountered and serious forms of ocular syphilis optic neuritis optic atrophy and interstitial keratitis are dis cussed below and in the chapter on Neuro syphilis In addition iritis chorioretinitis and rarely a gumma of the orbit or eye may develop as late manifestations of the infection Both iritis and chorioretinitis occur in association with many diseases other than syphilis and the syphilitic form of these ophthalmic disorders is in no way distinctive

Gummas Although the development of a gumma has been observed at one time or another in virtually every organ of the body these focal lesions of late syphilis seldom occur in tissues other than those of the skin bones liver testes or larynx It must be appreciated that it is not usually possible to establish with certainty that a particular lesion is a gumma either by the examination of biopsy specimens or by the demonstration of *T pallidum* in the af fected tissue *T pallidum* is notoriously diffi cult to demonstrate in most lesions of late syphilis and the histopathological picture of a gumma while characteristic of syph ilis may also be simulated by a number of other chronic granulomas From the stand point of diagnosis therefore a gumma is a chronic granulomatous lesion reasonably characteristic in appearance which de velops in a person with syphilis and which resolves with residual fibrosis within a few weeks of the institution of antisyphilitic therapy The results of the S T S are of great value in the diagnosis of a gumma with modern techniques the tests are al most invariably positive in high titer Con versely the finding of a negative S T S (with no history of previous antisyphilitic therapy) constitutes strong evidence against the possibility that a particular granuloma is syphilitic in origin

Skin In contrast to the multiple lesions of the skin which may appear during the course of infectious syphilis cutaneous gummas are usually localized to a single area The skin of the face neck and ex tremities is most frequently involved pre sumably because of the influence of trauma The lesion arises in or under the skin as a nodule which enlarges at so slow a rate that it produces no pain or tenderness The nodule may eventually break down forming a symmetrically rounded ulcera tion with an indurated base which is cov ered with a small amount of exudate Al though the individual intact nodules are reddish brown there is a gray blue colora tion along the periphery of the gumma which is sufficiently characteristic to be helpful in diagnosis The ulcerated or in durated lesions heal slowly and are replaced by a thin smooth scar which retains the configuration of the active process and is surrounded by a pigmented border If un treated a cutaneous gumma may persist in varying stages of activity for a period of months or even for several years Gummas of the skin may simulate a number of dis eases and are frequently mistaken for vari cose ulcers of the legs or for lupus erythe matosus (discoid type) of the face

Juxta articular nodules are firm subcu taneous gummas which may develop on the extensor aspects of the elbows or knees close to the insertion of the muscle The nodules seldom enlarge to more than 1 or 2 cm in diameter and rarely ulcerate

Skeletal System Gummatous lesions of the skeletal system develop in approxi mately 5 to 10 per cent of patients with late syphilis more commonly in Negroes than in whites The process may involve the periosteum the cortex or the medullary cavity The periostitis is primarily prolifera tive but in osteitis and osteomyelitis both destructive and proliferative processes are present together In syphilitic involvement of the skull the lesions are predominantly destructive in character

Syphilitic disease of bone is often mis taken for sarcoma tuberculosis or meta static carcinoma Gummas may be differ entiated from these other diseases by (*a*) the S T S which is almost invariably posi tive in high titer in the presence of syphilis

of bone (*b*) the appearance of the lesion in the roentgenogram (*c*) biopsy and (*d*) the response to antisyphilitic therapy

The finding of a negative S T S constitutes strong evidence against the diagnosis of osseous syphilis Moreover it is essential to realize that if a suspected lesion is an active gumma it will show evidence of healing within a few weeks of the institution of therapy Unless definite symptomatic improvement appears within a four week period therapeutic trial should be discontinued and a biopsy performed because of the possibility of neoplastic disease

Syphilis of the Liver Syphilis is a rare cause of clinically detectable disease of the liver and is discussed in the chapter on Diseases of the Liver

Gumma of the larynx develops occasionally in persons with late syphilis The chief clinical manifestation of this form of syphilis is the development of severe and persistent hoarseness in a person who is otherwise completely asymptomatic Gummas may closely simulate tuberculous or neoplastic disease of the larynx Therefore a therapeutic test should not be attempted until an effort has been made to exclude the presence of these more serious diseases

Gumma of the testicle or epididymis occurs rarely and is characterized by the development of a firm smooth occasionally nodular mass which slowly enlarges in size Testicular gummas seldom produce symptoms other than a dragging sensation caused by the weight of the mass As neoplasms arising from the testicle may grow and metastasize with great rapidity the physician must be unusually wary in order to avoid the serious error of performing a therapeutic test for syphilis in a patient with a malignant neoplasm

Gummatous Formation on Other Structures As mentioned previously the development of the localized gummatous lesion of late syphilis has been observed in virtually every tissue of the body Because of the rarity with which gummas appear in structures other than those noted above no attempt will be made to catalogue all the possible sites of involvement Nevertheless certain points should be emphasized

Gummas usually produce clinical manifestations similar to those caused by chronic infectious or neoplastic disease of a particular structure Therefore even in a patient known to have syphilis the physician should be slow to accept the diagnosis of gumma in a site of infrequent involvement until the possibility of neoplasm has been excluded (by biopsy or surgical exploration if necessary) Moreover even in patients who have been infected with syphilis the presence of a gumma is distinctly unlikely if the S T S is negative

SYPHILIS IN PREGNANCY

A woman infected with syphilis can transmit the disease to a fetus for an undetermined period of years after she has contracted the infection As would be anticipated the chance of intrauterine transmission of syphilis is greatest when the infection has been recently acquired and diminishes throughout successive pregnancies Infection of the fetus usually occurs after the fifth month of pregnancy and may result in spontaneous abortion miscarriage a stillborn fetus or a fatally ill infant

Prenatal Syphilis The clinical manifestations course and diagnostic problems presented by syphilitic infection in infancy and early childhood are beyond the scope of the present article The clinical manifestations and the course of prenatally acquired syphilis in *adults* are with few exceptions essentially the same as in acquired infections of comparable duration The unique features of the prenatal variety are the frequency of *interstitial keratitis* and the virtual absence of aortic involvement Ophthalmalogical texts should be consulted for a discussion of interstitial keratitis Localized gummatous lesions occur in prenatally acquired syphilis and are identical in every respect with the gummas of late syphilis acquired in adult life Skeletal involvement is not uncommon and in the form of osteitis or periostitis may produce saddle nose or sabre shins A nongummatous form of skeletal involvement which is unique to prenatally acquired syphilis is the characteristic malformation of the teeth described originally by Hutchinson The changes are most conspicuous in the central incisors which are unusually small widely spaced notched and less broad at the cutting edge than at the gum margin A rarely encountered syndrome of *Hutchinsonian teeth interstitial keratitis* and *eighth nerve deafness* (caused by meningeal involvement) is known as *Hutchinson's triad* and is considered to be unequivocal evidence of the presence of prenatal syphilis

Pregnancy Adult women with prenatally acquired syphilis may transmit the infection to their offspring during pregnancy Such third generation syphilis is extremely rare but seemingly indisputable instances of its occurrence have been reported More often an apparent instance

of this phenomenon is the result of syphilitic infections contracted independently by a mother and her daughter and the subsequent intrauterine transmission of the disease by the latter

SEROLOGICAL DIAGNOSIS OF SYPHILIS

The serological tests for the presence of *syphilis reagin* (S T S) assume a greater or lesser importance in diagnosis depending upon the type of syphilitic infection which is under consideration In infectious syphilis the serological tests are distinctly secondary in importance to the demonstration of *T pallidum* by darkfield microscopy In certain varieties of cardiovascular and neurosyphilis the serologic tests are chiefly of value as an additional confirmation of the clinical diagnosis In the great bulk of infections observed by the practitioner however the diagnosis of syphilis can be established only by serological testing It is essential therefore that an S T S be obtained as part of the routine of the initial examination of every patient It is equally important that the results of such tests be subjected to proper interpretation

The Wassermann test and the other tests designated by proper names are all based on the same immunological phenomena and all detect the same substance *syphilis reagin* In a very real sense all of these tests are nonspecific This fact presents no difficulties when the S T S is employed to *confirm* a diagnosis of syphilis made by clinical examination or from the patient s history The nonspecificity becomes of the greatest importance however *when a positive S T S represents the sole indication that a patient might have syphilis* For in addition to syphilis and the other treponemal infections (yaws pinta bejel) there are other states not necessarily infectious which may give rise on occasion to a positive S T S Such results of serological testing are designated *biological false positive reactions* or B F P The incidence of these reactions has not yet been defined but it has been credibly estimated (Moore) that in certain highly selected populations in the U S the incidence may approach 50 per cent

The finding of a positive S T S in a person with absolutely no clinical or historical evidence of syphilis is thus to be regarded as a highly significant lead but it does not certainly establish the presence of syphilis

Situations in which it is well for the physician to be particularly wary of the diagnosis of syphilis solely on serological evidence are (*a*) the presence of a positive S T S in a patient who is suffering or convalescing from an acute infection (*b*) the finding of a positive S T S in a patient who has had a recent negative test and whose sexual partners are nonsyphilitic and (*c*) the finding of a series of doubtful (i e "one to three plus") S T S possibly punctuated by an occasional positive in a person who credibly denies having experienced any previous manifestations of syphilis or antisyphilitic therapy

The problem of the person with the recent acute infection is relatively simple as the false positive S T S which occurs in this setting are usually transient The treponemal immobilization reaction of Nelson can be of immense help and it is current practice to regard all S T S reactors whose serum is negative by the immobilization test as being truly nonsyphilitic Unfortunately however relatively few laboratories are presently able to perform the treponemal immobilization test on a service basis Hence in most circumstances the problem must be managed by the exercise of arbitrary judgment

Accordingly whenever the standard S T S are repeatedly positive in a person with no clinical or historical evidence of syphilis or the other states mentioned above it is advisable to treat the patient as if early latent syphilis were present (see below) For a detailed discussion of this question of the significance of serological tests for syphilis the reader should consult the reports by Moore and Mohr and by Davis

TREATMENT

Early Syphilis The goal of antimicrobial therapy in syphilis is to effect a drastic reduction of the population of *T pallidum* to a census readily manageable by the host In early syphilis (infectious and early latent) attainment of this goal by penicillin is followed in 85 to 90 per cent of infected persons by an apparently complete disappearance of *T pallidum* from the body In the remainder after disappearance of the acute manifestations the infection survives into the late latent stage or reappears as an infectious or neurological relapse The possibility of such relapse can be minimized by continuation of the antimicrobial therapy for a matter of months In such circumstances it is highly unlikely that the continued therapy *per se* eradicates the persisting *T pallidum* On the contrary eradication during prolonged therapy is presumably accomplished either by the defenses of the host or more probably by

the natural death of the parasites after their prolonged physiological confinement

As the incidence of relapse after short term therapy is so relatively low it seems impracticable and indeed inadvisable to subject all patients with early syphilis to the months of treatment necessary for only a few Accordingly an acceptable procedure is to treat all patients with early syphilis with only a single large dose of one of the long lasting preparations of penicillin

A satisfactory regimen for this purpose consists of the intramuscular injection at multiple sites of a total dose of 2 400 000 units of one of the long lasting penicillins The entire dose may be administered at one visit or may be divided over two successive days The most satisfactory preparation is *benzathine penicillin G fortified with procaine penicillin G* which is available under a variety of proprietary names Procaine penicillin in oil containing 2 per cent aluminum monostearate can be substituted in the same dosage

In the relatively remote event that relapse or other failure of treatment should be detected on subsequent observation the patient could either be retreated with the above described regimen or could be given 900 000 units of procaine penicillin per day on eight successive days excluding Sundays In situations in which it is desired to reduce the chance of relapse to a minimum it is advisable to prolong therapy for a six month period by the addition of 300 000 units of procaine penicillin once or twice weekly to either of the two short term regimens

A number of other drugs notably chloramphenicol and the tetracyclines are relatively imperfect substitutes for penicillin in the treatment of syphilis Regimens for the use of these other drugs have not been clearly defined Hence when penicillin can not be used it would seem advisable to administer chloramphenicol or a tetracycline drug orally for a two week period in a total daily dose of 3 0 gm with unusually meticulous clinical and serological follow up observations thereafter

Course of Early Syphilis Under Treatment In early syphilis an acute exacerbation of any visible lesions may become evident within six to ten hours of the initiation of treatment This exacerbation soon after the institution of antimicrobial therapy is designated the *Herxheimer reaction* and occurs to some degree in the majority of patients with early syphilis It is seldom sufficiently emphasized that the intensity of a Herxheimer reaction reflects the intensity of the syphilitic inflammation before treatment Thus lesions which are poor in *T pallidum* are less likely to develop an acute exacerbation following the start of therapy than the infectious lesions of early syphilis The duration of the reaction is short (two to four hours) and in early syphilis the phenomenon is in no way harmful

The rate of disappearance of *T pallidum* and the healing of the external lesions are modified by their number and size In general within twenty four hours of the start of therapy *T pallidum* is no longer demonstrable in the lesions and the latter show evidence of the onset of resolution During the succeeding week healing proceeds rapidly All but the most unusually extensive processes are completely healed save for residual pigmentation or scarring within seven to ten days after the start of therapy

At this point the patient presents little or no clinical evidence of syphilitic infection but unless treatment was started before the development of seropositivity the serological tests are still positive

During the first six months after the start of treatment the patient should be seen at intervals of two weeks and questioned for symptoms suggestive of mucocutaneous ocular or neurological relapse Moreover the questioning should be supplemented by a complete examination of the skin oral cavity genital and perianal regions superficial lymph nodes anterior eye and fundus cranial nerves and the tendon reflexes of the extremities Material from a lesion which makes its appearance should be examined by darkfield microscopy At the same two week interval a specimen of blood should be obtained for serological testing When facilities are available the blood specimens obtained before during and after treatment should be tested in serial dilution if the usual qualitative test is positive (*i e* four plus) A pronounced fall in titer (*e g* positive when diluted 1 to 128 changed to positive when diluted 1 to 4 and negative on further dilution) may be detectable at a time when the usual qualitative test would be reported simply as *positive* (*i e* four plus) Even with the aid of quantitative tests a change in the S T S may not become evident until the third or fourth month after the start of treatment Between the third and sixth month after the institution of therapy the serological reactions gradually become negative in the majority (approximately 80 per cent) of treated cases In a small number of patients (5 or 10 per cent) the

reaction may not be consistently negative at six months but the titer will have fallen considerably and the reaction will become completely negative by the ninth or twelfth month after the start of treatment In the remaining group of infected persons (5 or 10 per cent) despite some fall in titer during and after treatment the serological tests for syphilis will be repeatedly positive (*i e* four plus) one year after the institution of therapy Some of this latter group may attain seronegativity during the second post treatment year

In a small proportion of treated infections persistently positive serological reactions may show a steady increase in titer or the reaction once negative will again become positive In evaluating such sero relapse it is essential that the physician realize that minor fluctuations below the range of complete positivity (*i e* so-called "one plus to three plus reactions) are merely a reflection of the day to-day variation in the sensitivity of the serological test in the laboratory and have no significance in respect to a change in the serologic status of the patient Only a change from complete negativity to complete positivity or a two fold change in titer can be considered as definite evidence of serological relapse Although clinical relapse does not invariably accompany or follow serological relapse a correlation between the two phenomena is so frequent that they have an identical significance in terms of therapy

A satisfactory serological response to treatment in early syphilis may thus be defined as complete or virtually complete seronegativity six months after treatment was started It is probable that many persons who fail to show such prompt serological reversal require no further therapy In the present state of knowledge however it is advisable to regard all such cases as therapeutic failures and to reinstitute therapy

Six months after the start of therapy it is essential to determine the total cell count total protein colloidal gold and S T S of the *cerebrospinal fluid* In the event that abnormalities are present treatment for early neurosyphilis should be instituted according to the principles discussed in a following chapter If the cerebrospinal fluid is normal at this time it is necessary to examine it on one more occasion after an interval of one year *i e* eighteen months after therapy

If at six months after the start of therapy for early syphilis the patient presents no evidence of relapse on clinical or cerebrospinal fluid examination and the blood serological tests have shown a satisfactory response the interval between examinations (clinical and serological) may be extended to one month The procedure at the time of each visit should be exactly the same as when the patient was examined at fortnightly intervals and the monthly examination should be continued for one year The clinical and serological follow up should be continued for a total period of five years but the interval between examinations may be gradually lengthened to three to six months after the first eighteen months of observation have been completed

Prognosis of Early Syphilis Following Penicillin Treatment The incidence of either biological cure (*i e* complete eradication of *T pallidum*) or of permanent latency which may be expected following the use of present-day methods for the penicillin treatment of early syphilis cannot yet be stated with precision In broad terms it can be said that biological cure is apparently attained in 85 to 90 per cent of the persons who receive one course of treatment and in a substantial proportion of those who require retreatment The ultimate outcome of the infection among patients with apparent biological cure two or three years after treatment is almost uniformly excellent A few patients with early syphilis will fail to become serologically negative If they have been adequately treated including a second course of penicillin treatment for the seroresistance and have no evidence of syphilis other than a low titer on quantitative serological test they may be safely followed without further treatment

Relapse and Reinfection in Early Syphilis Post treatment relapse of early syphilis is a phenomenon which if unrecognized has serious implications The incidence of complicating lesions in the eye or nervous system appears to be appreciably higher in the case of post therapy relapsing infections than in the course of relapsing untreated syphilis Moreover opportunity for transmission of the infection is enhanced as the person may not appreciate that the cutaneous or mucosal lesions of relapse are related to the treated venereal infection of several months previously

Reinfection probably accounts for a considerable number of the treatment failures The patient is cured of his infection before he has mobilized resistance to *T pallidum* and hence can become reinfected With the old long term arsenical and bismuth ther

apy the patient was protected from reinfection while he was under treatment and presumably also had developed considerable immunity by the time therapy was completed

Late Latent Syphilis It is probable that once true latency (*vide supra*) has been established there is no need for the administration of antisyphilitic therapy Moreover the possibility exists that the organisms which persist within the host after the development of true latency are not particularly susceptible to antimicrobial therapy Unfortunately there is no way by which apparently latent syphilis can be distinguished from active disease of the aorta or other viscera which has not progressed to the point of clinical recognition Thus the physician has no choice other than to treat all persons with late latent syphilis

From the preliminary experience in the treatment of early syphilis with penicillin and from the available knowledge of the course of the infection once late latency has been established it would seem that regimens which constituted adequate therapy for early syphilis would be at least equally effective in the treatment of late latent syphilis Because the problem with late latent syphilis is less urgent however it is permissible to use a regimen of 600 000 units of procaine penicillin administered twice weekly for a four week period

Course Under Therapy and Prognosis As by definition persons with late latent syphilis exhibit no clinical evidences of infection they will show no change in clinical status as a result of successful therapy In an individual patient with late latent syphilis a precise evaluation of the result attained by therapy or natural immunity can only be made by following the patient throughout his entire lifetime Until sufficient time has elapsed to permit a long term evaluation of the results of the penicillin therapy of late latent syphilis therefore the expected outcome of the infection in a person treated with penicillin can only be surmised from the results of penicillin therapy in other forms of syphilis A reasonable prediction would be that less than 2 per cent of patients with late latent syphilis who are properly treated will subsequently develop a serious manifestation of late syphilis The few who do exhibit evidence of progression despite theoretically adequate treatment will be chiefly those in the older age groups who had well established but clinically unrecognizable aortitis at the time of the treatment of the apparently latent syphilis

Serological Reversal in Late Latent Syphilis In late syphilis (including the latent variety) the serological tests do not reverse to normal after treatment so readily and uniformly as they do following the therapy of recently acquired infections This frequent failure of the serological tests to become normal is designated *seroresistance* There are two important facts concerning seroresistance which must be fully appreciated by the physician (1) There is no reason to believe that the phenomenon of seroresistance alters the outcome of the treated infection in any way (2) Seroresistance cannot be influenced by additional therapy Once it is established that a patient with late latent syphilis has received a proper regimen of therapy it is as irrational to continue therapy because of a persistently positive S T S as it would be to persist with antituberculous chemotherapy merely because of the continued presence of a positive tuberculin reaction The physician should realize that the laity almost without exception hold the erroneous notion that a positive S T S signifies the actual presence of *T pallidum* in the particular specimen of blood which was tested Therefore it is important to explain in understandable terms the true significance of serological tests to each patient who is infected with syphilis It must be appreciated that seroresistance by definition is the phenomenon observed only in *latent* syphilitic infections The persistently positive serological tests in persons with obvious progressive lesions of the aorta or nervous system are not to be considered as examples of seroresistance

Examination of the Cerebrospinal Fluid in Late Latent Syphilis In contrast to the situation which exists in early syphilis the cerebrospinal fluid is examined *before* the institution of therapy in late latent syphilis for a normal fluid is one of the prerequisites for the diagnosis of latency In the event that a latent infection has been proved to be really late *i e* of more than four years duration subsequent examinations of the cerebrospinal fluid are not necessary In those instances in which it is impossible to determine the duration of the infection and hence the possibility of early latent syphilis cannot be excluded the cerebrospinal fluid should be reexamined eighteen months after the institution of therapy

Treatment of Gummas The penicillin regimens appropriate for late latent or for early syphilis are entirely adequate for the treatment of a gumma If aortic or neurosyphilis is also present it should receive

precedence in the choice of therapy and a penicillin regimen appropriate for aortic or neurosyphilis would also be appropriate for a gumma When a gumma is strategically located as in the larynx it is advisable to administer only two 25 000 unit doses of penicillin on the first day of treatment In this way the intensity of a Herxheimer reaction might be modified even though its occurrence cannot be completely prevented The complete regimen can then be started on the following day Within the first week of treatment there will usually be subjective and objective evidence of improvement in the status of the lesion Resolution of the lesion or lesions is steadily progressive but the time required for complete healing will vary from several weeks to several months depending upon the original size of the gumma Once the lesions are completely healed the subsequent course and the management of the patients are the same as in late latent syphilis

Treatment of Syphilis in Pregnancy An S T S should be obtained on every pregnant woman during the first and last trimesters of pregnancy and any woman who has had syphilis should be evaluated as to the need for antisyphilitic treatment with each pregnancy Formerly treatment was repeated with each pregnancy This is no longer deemed necessary and the present practice is to allow a pregnant woman to reach term untreated provided that she has received theoretically adequate therapy in the past shows no clinical evidence of active syphilis and is seronegative

Early syphilis in the pregnant woman carries the greatest risk of infection of the fetus Nevertheless with penicillin a normal infant can be expected even if the disease is discovered late in pregnancy The penicillin regimens recommended for early syphilis are satisfactory for the treatment of syphilis in pregnancy If the infection is not discovered until after the thirty second week of pregnancy however it is advisable to administer 300 000 units of procaine penicillin three times daily for at least eight days

Treatment of Prenatally Acquired Syphilis Except for interstitial keratitis the treatment of the various manifestations of prenatally acquired syphilis which are first recognized during adult life is the same as in the corresponding situations with syphilis contracted during adult life *Interstitial keratitis* is a potentially serious complication which should be treated promptly and intensively with penicillin and cortisone or corticotropin Procaine penicillin 300 000 units intramuscularly should be administered each day for a two week period Preliminary observations indicate that cortisone and corticotropin systematically are equally effective but apparently no more so than cortisone when used locally Whenever possible interstitial keratitis and the other ocular manifestations of syphilis should be treated in consultation with an ophthalmologist

INDIVIDUAL PROPHYLAXIS AND THE PREVENTION OF SYPHILIS

The most effective prophylaxis against syphilis is the use of a condom during sexual intercourse and a thorough cleansing of the genitalia and adjacent areas with soap and water immediately thereafter These measures afford an appreciable amount of protection to either sex against the direct genital transmission of the infection There is no efficacious method of protection against transmission by other bodily contacts The most practicable method for the *prevention* of syphilis among a civilian population is to effect a reduction in the *prevalence of infectious syphilis* by the prompt recognition and proper therapy of all persons with recent infections In this way the incidence of new contact infections can be sharply reduced

PSYCHOLOGICAL AND SOCIAL ASPECTS OF SYPHILITIC INFECTION

The mechanics of the diagnosis and treatment of syphilis are simple and require but little of the physician s time Not infrequently however the patient s discovery that he or she has syphilis immediately gives rise to problems which occasion considerable mental distress Athough these problems appear uniquely insolvable to the person concerned they can usually be settled satisfactorily by the physician who is willing to devote the time It is not sufficient for the physician merely to "answer any questions" Frequently a reticent patient will cherish all manner of unwarranted fears about the effects of the infection on himself or his intimates without betraying such fears to his physician Therefore at the same visit at which the diagnosis of syphilis is announced it is essential that the physician undertake an active discrediting of the folklore of syphilis and an honest presentation of the facts and potentialities of syphilitic infection The questions of transmissibility to others the risk of neurosyphilis the chances of

having nonsyphilitic children and the significance and expected course of the serological tests should be discussed in detail The circumstances under which it would be proper for the patient to marry depend upon the stage of the infection In general it is not advisable for the patient to marry a nonsyphilitic person until the danger of infectious relapse is minimal *i e* one year after an adequate course of penicillin therapy An infection of more than four years duration should not constitute a barrier to marriage from the standpoint of transmission of infection to the spouse The presence of neurosyphilis however constitutes a certain economic liability and in decisions on the advisability of marriage should receive exactly the same consideration as any other physical handicap Obviously if the physician knows or suspects that a patient has paresis every effort should be made to prevent marriage

In marital and premarital problems the physician should exert all his influence to have the patient inform spouse or fiancee of the diagnosis of syphilis Although the patient (and some physicians) frequently believe that the announcement to the marital partner that the patient has syphilis will 'break up the marriage such fears are almost invariably unwarranted In the unusual event that a patient with *potentially infectious* syphilis refuses to inform the marital partner the physician should undertake to do so

WALSH McDERMOTT

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Nonsyphilitic Treponematoses

For many years it has been recognized that there are a number of disease syndromes occurring principally among the more backward peoples of warm countries that are syphilis like in their general course and symptomatology These syndromes have both clinical and epidemiological features which still make it useful to give them distinguishing names such as *yaws bejel pinta* and *endemic syphilis*

It is now known that the etiological agent of each of these disease syndromes is a spiral microorganism which is indistinguishable morphologically from the treponeme of syphilis *Treponema pallidum* Moreover infected persons develop serum antibodies—Wassermann antibody and treponemal immobilizing antibody—just as do persons with syphilis significant degrees of cross immunity can be demonstrated experimentally and each disease responds well to the usual antisyphilitic drugs such as penicillin and the arsenicals

On the basis of the foregoing considerations it is becoming common practice to refer to this group of diseases including syphilis as the *treponematoses* Nevertheless real clinical and biological differences do exist among the various diseases belonging to this general group differences which bear on problems of diagnosis treatment prevention and community control From a more academic standpoint the relationship of these diseases one to another presents absorbing problems to the medical biologist interested in microbial variation and mutation as influenced by climate race and other ecological factors

It is clear from clinical epidemiological and laboratory investigations that these are not simply different manifestations of the same disease for each disease will reproduce itself under controlled experimental conditions Laboratory experiments suggest however that long continued exposure of infected hosts to different environmental conditions eventually results in modification of certain biological characteristics of the particular treponemes To what extent this same phenomenon may occur in nature is still only a matter for speculation

Finally to complete and at the same time confuse the picture of this group of diseases there is a naturally occurring disease of domestic rabbits designated venereal spirochetosis caused by a treponeme (*T cuniculi*) which is morphologically indistinguishable from the human pathogenic

treponemes The disease is likewise characterized by the development of Wassermann and treponemal immobilizing antibodies ready response to antisyphilitic drugs and some degree of reciprocal immunity to syphilis and yaws No human infection with this treponeme has been recorded

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Yaws

Definition Yaws is a specific disease caused by a spirochetal organism *Treponema pertenue* It is largely limited to tropical countries and is characterized by an initial cutaneous lesion followed by a multiple papular granulomatous skin eruption and in some instances by late destructive lesions of the skin and bones Lesions of the soles of the feet are especially common Among synonyms for the disease are frambesia tropica pian (French) bouba (Spanish American) and parangi (Ceylon) Many others are listed by Hermans (1931)

History The earliest reliable accounts of yaws now available date to the seventeenth century Since Negroes were brought from Africa to the West Indies as early as 1510 it cannot be determined whether yaws was introduced into the Americas through this means or whether the disease already existed among the native tribes Undoubtedly it was prevalent among slaves imported from Africa and by the eighteenth century yaws had become a serious problem on plantations in the West Indies

Etiology The spirochete of yaws (*T pertenue*) was first described by Castellani in 1905 soon after the discovery of *T pallidum* by Schaudinn The organism measures from 8 to 20 μ in length and about 0 2 μ in diameter It has six to fourteen closely placed spirals and morphologically is indistinguishable from the spirochete of syphilis It is best seen in the fresh state by darkfield illumination The organism stains with difficulty

Among laboratory animals *T pertenue* is pathogenic for monkeys rabbits and hamsters subclinical infection only is produced in mice rats and guinea pigs At ordinary temperatures the organism survives for only a few hours when removed from a living host in special media it will survive for several days but multiplication does not occur It remains virulent for years when stored at −70 C in 15 per cent glycerin

Epidemiology *Distribution and Prevalence* Yaws as an endemic disease is practically limited to the tropics It is particularly common in equatorial Africa the West Indies parts of India Ceylon the Philippines Indonesia and throughout the entire group of Southern Pacific islands Endemic foci occur in parts of Brazil and Colombia in South America and in several countries of Central America Only sporadic cases have been reported from North America and Europe The disease is not distributed uniformly however even within the tropics The situation as found by the epidemiological studies of the Jamaica Yaws Commission (Turner Saunders Kumm and others 1935 1937) is interesting and may be representative of that in other countries In that country the distribution of yaws is uneven Areas of high prevalence lie within a few miles of communities in which it is rarely encountered and there is a close correlation between its prevalence and certain environmental factors Where yaws is common there is practically always a heavy rainfall and a fertile moisture holding soil supporting an abundant vegetation

It is principally a disease of rural peoples the lowest social and economic groups showing the highest attack rate There is no clear evidence of racial immunity

Yaws is usually acquired in childhood but no age is free from the risk of infection In one community in Jamaica (Bath) prevalence rates rose from 26 per cent among all children under five years of age to 75 per cent among those ten to fourteen years of age Approximately 90 per cent of all persons found to have infectious lesions were under twenty years of age

Transmission Yaws can be transmitted by direct person to person contact but it is probable that nonbiting insects also play a role in the spread of the disease There is no evidence for the existence of an animal or avian reservoir The initial yaws lesion which develops at the point of implantation of the spirochete is frequently observed at the site of a previous injury and is located on the lower extremity in the majority of cases Sexual transmission rarely occurs Transmission from mother to child *in utero* has not been established

Since earliest times the possibility of transmission by insects has been recognized Studies in Jamaica (Kumm and others 1935 1936) indicate that in this country a small gnat *Hippelates pallipes* is a likely mechanical vector

Pathology Histologically the cutaneous papule or frambesioma shows marked epi



FIG 39 Yaws in a child showing generalized frambesiform lesions

thelial hyperplasia elongation of the papillae exudation of leukocytes on or near the surface with many lymphocytes and plasma cells in the dermis Silver stains show spirochetes in large numbers in the epidermis and more superficial dermis The late ulcerative lesions of yaws are histologically similar to syphilitic gummas On the whole the histological criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are unreliable (Ferris and Turner 1937) The occurrence of visceral lesions in yaws is still debated Evidence is accumulating that the aorta is sometimes involved (Choisser 1929 Chambers 1936 Weller 1937) With possibly rare exceptions the central nervous system is not affected

Clinical Manifestations *Skin* Within two to eight weeks after infection the initial or primary lesion appears at the point of implantation of yaws spirochetes This lesion is a granuloma and may develop into a large cauliflower like growth from which *T pertenue* can be recovered There is accompanying enlargement of the regional lymph nodes The initial lesion usually persists for several months and heals with scar formation

During the first weeks of the disease *T pertenue* gains access to the blood stream and symptoms attributable to generalization of the organism soon become manifest These consist of widely distributed skin lesions often enlargement of the superficial lymph nodes bone and joint pains and in some cases clinically recognizable lesions of these structures Mild constitutional symptoms such as low grade fever loss of appetite and slight loss of weight may occur but in many cases the general health of the person is not materially affected Within one or two weeks after development of the initial lesion blood serological tests similar to those used in the diagnosis of syphilis (Wassermann Kahn Eagle Hinton) become positive increase rapidly in titer and remain positive for many years unless rendered negative by specific therapy The treponemal immobilization test and other specific treponemal tests also become positive and remain so for many years in untreated patients

The generalized rash may comprise at first only scaly macular lesions More commonly however from the beginning the rash is polymorphous comprising scaly macules folliculopapules papules and most prominent of all large granulomas—the yaw or frambesioma which is characteristic of this disease As the disease progresses the frambesiform lesions become more numerous and larger the patient with a fully developed generalized frambesiform rash presents an arresting picture one which can scarcely be confused with any other disease (Fig 39) The individual lesion stands out from the skin level like a giant wart measuring 0 5 to 4 0 cm in diameter The surface of the lesion which may be covered by a crust is granular like the surface of a raspberry—hence the name frambesia Serum from the lesion yields large numbers of motile *T pertenue*

After several months retrogression of the generalized lesions may begin The smaller lesions heal and the large frambesiform lesions tend to become smaller and less numerous but it may be many months before they have entirely disappeared Even then relapses are not uncommon so that infectious types of lesions may be present off and on for several years after the onset of the disease Eventually a stage of latency is usually reached but this stage may likewise be interrupted at intervals by the occurrence of more bizarre types of lesions in which *T pertenue* cannot be readily demonstrated

After several years have elapsed skin lesions similar to the syphilitic gumma may

occur These so-called "late lesions" are characterized by tissue destruction and ulceration often involving large areas of skin and subcutaneous tissue *Treponema pertenue* cannot be found but other types of spirochetes notably *Borrelia refringens* may be present Healing often leads to extensive scarring which if located in the region of a joint may lead to contractures

Lesions of the soles of the feet are common and account for a good deal of the disability from the disease Two types which may occur alone or together are recognized One type consists of one or more eroded papules somewhat analogous to the frambesiform lesion of the skin Instead of protruding above the plantar surface however the papule lies at the base of a small opening in the sole and is exquisitely tender Serum from these lesions is usually rich in *T pertenue* Like other infectious lesions plantar papules are observed most commonly in the first years of the disease

The other type of plantar lesions consists of widespread hypertrophy stripping or fissuring of the superficial layers of the sole and less frequently of the palms giving rise to a curious mottled pattern characteristic of yaws There is usually no ulceration and *T pertenue* cannot ordinarily be demonstrated Plantar hyperkeratosis the so-called "crab yaws" may occur at almost any period during the course of yaws it has been observed in patients soon after development of the generalized rash as well as twenty years or more after infection

Bones In the Jamaica series bone lesions were observed in about 15 per cent of all patients showing active manifestations On the basis of roentgenographic changes two types are recognized not infrequently both types are present simultaneously In the one type periosteal proliferation similar to that seen in syphilis is the most prominent feature In the other type areas of rarefaction or destruction in the shafts of the long bones are observed These areas are round or oval and usually multiple with a surrounding zone of increased density Clinically the patient complains of pain in the affected region and there may be tenderness and swelling of the overlying soft parts (Goldman and Smith 1943 Helfet 1944) The bones of the forearms legs and hands seem most often to be affected involvement of the skull pelvis and spine is rare Both periostitis and osteitis may occur either in association with infectious skin lesions or in later years after the generalized skin lesions have healed

Other Yaws Lesions Among the less common but more spectacular lesions of yaws are gangosa goundou and juxta articular nodules In *gangosa* the cartilaginous and bony structures of the nose are partially or completely destroyed by a late ulcerative process Cutaneous leishmaniasis may cause somewhat the same picture *Goundou* is an egg shaped paranasal enlargement arising from the superior maxillary bone The tumors may be sufficiently large to interfere with vision (Strong and Shattuck 1930) *Juxta articular nodules* are firm freely movable painless subcutaneous fibroid tumors situated in proximity to a joint

Differential Diagnosis A case of yaws with typical generalized lesions cannot easily be confused with any other disease Individual lesions may resemble those of secondary syphilis or cutaneous leishmaniasis but when the case as a whole is considered little difficulty should be experienced Demonstration of the treponeme in skin lesions serves to differentiate yaws from all conditions except those of the syphilis group Late ulcerative lesions of yaws are often indistinguishable from the tertiary lesions of syphilis The late effects of yaws ulcerative lesions contractures partial amputation of digits may resemble the lesions of leprosy In areas where yaws is common serological tests for syphilis are of limited value in differential diagnosis

Prognosis The disease is rarely directly fatal except in young infants Without treatment the disease leads to months of partial incapacity with the possibility of relapses over a period of many years A not inconsiderable proportion of infected persons apparently go on after many years to spontaneous clinical and serological cure The indirect mortality from the disease because of secondary infection of cutaneous ulcers or bone lesions is probably higher than is commonly supposed In areas of high yaws endemicity a substantial proportion of the beds in chronic disease hospitals and poorhouses are occupied by patients whose disability stems primarily from yaws With early treatment the prognosis is entirely favorable

Treatment and Control Yaws responds to the same therapeutic agents that are effective in syphilis it is commonly believed that smaller amounts of drugs are required for yaws but this has not been fully documented Penicillin is the drug of choice the tetracyclines have some therapeutic action but are much less effective than pen



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icillin Use of the arsenical drugs or bismuth is not recommended

Ideally the treatment of yaws should be similar to that of early syphilis in which 2 400 000 units of long lasting penicillin is given intramuscularly at multiple sites One half of this dose is given to children under ten years of age Benzathine penicillin G fortified with procaine penicillin G which is available under a variety of proprietary names is the most satisfactory preparation but procaine penicillin in oil containing 2 per cent aluminum monostearate can also be used in the same dosage In large scale campaigns conducted under the auspices of the World Health Organization a standard dose of 1 200 000 units of one of the foregoing preparations for adults and half that amount for children less than ten years of age have been used with success

The response to penicillin is dramatic Initial and generalized lesions commonly become darkfield negative for *T pertenue* within forty eight hours and healing is complete within one week Serological titers decline rapidly but a substantial proportion of patients may still show a low titer serological test after six months

Late skin lesions as a rule respond promptly to antiyaws drugs but the more chronic lesions of the skin and bones may require local surgical treatment in addition to chemotherapy

The control program developed by the Jamaica Yaws Commission and subsequently extended and widely applied by the World Health Organization comprised the following (1) survey of the whole population of an area for the purpose of detecting all infectious cases (2) treatment of all cases and the contacts of infectious cases (3) periodic resurveys of the area in order to detect and promptly treat new infections which may arise Since more than 90 per cent of the infectious cases in most areas occur among persons less than twenty years of age it is to this portion of the population that control efforts are particularly directed

Prophylaxis No methods of artificial immunization are available In regions where yaws is prevalent the chances of infection can be reduced by avoiding minor injuries to the skin and by protecting all open wounds and abrasions from contamination by flies Children with infectious lesions should be excluded from school until rendered noninfectious by treatment Efforts to control insect vectors are not practicable at the present time

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Bejel

Bejel is a chronic infectious disease of the treponematosis group occurring principally among seminomadic inhabitants of the Arabian Peninsula Asia Minor and the Middle East It is a family disease the infection being acquired usually in childhood with subsequent transmission to adults living in the same tent unless these have been protected by previous infection Drinking utensils often constitute the vehicle of transmission and initial lesions are particularly common about the lips and within the oral cavity Serological surveys indicate that as high as 90 per cent of the inhabitants of some villages are affected

The evolution of the disease follows much the same pattern as that in syphilis and yaws Generalized lesions tend to be confined to the oral cavity and the mucocutaneous borders of the lips genitalia and anal regions The bejel treponeme which is morphologically indistinguishable from *T pallidum* can be readily demonstrated in early lesions by darkfield examination Bone lesions are common in both the early and late stages roentgenographic examination shows the changes to be similar to those observed in yaws Late lesions of the skin and gummatous involvement of the palate and nasal septum are also common in untreated cases No definitive data are available on the occurrence of visceral lesions

Bejel is an important cause of chronic illness in endemic areas but penicillin is as effective in bejel as in the other treponematoses In the control campaign initiated by the World Health Organization in Iraq good clinical results were obtained with penicillin in aluminum monostearate and oil in one dose of 1 200 000 units given

intramuscularly A second dose at an interval of three to seven days was given to those with osseous involvement While the immediate results were good it is not known what proportion of infected persons was cured by this treatment

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Pinta

(*Mal del Pinto Carate*)

Definition Pinta is a chronic endemic infectious disease characterized by dyschromic papular skin lesions which eventually become depigmented splotches

Etiology The disease is caused by a spirochete *Treponema carateum* (also *T herrejoni*) which is morphologically indistinguishable from *T pallidum* This spirochete can be demonstrated in the initial and generalized papular lesions by darkfield examination but not in the depigmented spots It has not been successfully propagated in laboratory animals or cultivated *in vitro*

Epidemiology Pinta is endemic in localized areas in Central America and the tropical portions of South America It has also been reported from the West Indies tropical Africa and various islands and countries of the South Pacific Pinta is biologically closely related to syphilis yaws and other members of the treponematosis group of diseases and in these areas certain diagnostic confusion between pinta and yaws is encountered

There is no racial immunity Transmission is usually by direct person to person contact Intrauterine transmission is believed not to occur Pinta is acquired mostly by children and young adults but because of its chronic nature many older persons exhibit signs of the disease

Pathology Active lesions appear to be confined to the skin and lymph nodes The initial and generalized papular lesions are similar histologically being characterized by thickening of the epidermis dense infiltration of lymphocytes and plasma cells into the dermis with foci of intracellular edema Perivascular infiltration is usually present The wide variation in the color of the lesions is a reflection of the degree of vascularity migration of the chromatophores into the more superficial layers of the skin and natural racial variation in skin pigmentation As lesions grow older there is a progressive decrease in vascularity cellular infiltrate and pigment

Symptomatology In a series of twenty eight purposeful inoculations of volunteers Leon Blanco found the usual incubation period to be fourteen to twenty days The initial or primary lesion is papular and enlarges slowly often becoming psoriasiform in appearance with smaller satellite papules When present alone it may be mistaken for psoriasis or lichenified eczema and its true nature can be established with certainty only by demonstration of *T carateum* The regional lymph node is usually enlarged and *T carateum* can be recovered by aspiration

The secondary stage which develops in five to twelve months after infection is characterized by a generalized eruption of macules or miliary papules called pintids which are often pinkish or violaceous and slightly scaly Most of these lesions heal but some enlarge and coalesce to form patches resembling psoriasis or lichenoid eczema They are particularly common on the face and other exposed parts of the body These lesions are exceedingly chronic and may last for years often remaining darkfield positive for *T carateum* all the while Itching is not a prominent symptom Hyperkeratosis of the soles and palms also occasionally occurs

It is this tertiary or dyschromic stage in which the characteristic symptomatology of pinta is observed When the low grade inflammatory process is still present the lesions usually exhibit some color sometimes a dull red or violet but more often a leaden or slate blue As time goes on the active process subsides the skin becoming atrophic and white because of the loss of pigment In some patients considerable disfigurement occurs from the extensive areas of vitiligo

Standard serological tests for syphilis are usually negative during the primary stage of the disease but become positive soon after the appearance of generalized lesions In the later stages of the disease the serum of nearly all patients gives a positive test often in high titer Immobilizing antibody to *T pallidum* is also present The only constitutional symptoms are those attributable to a mild chronic infection Reports of examination of the cerebrospinal fluid have yielded conflicting results a few observers reporting an increase in cell count in some cases Likewise the occurrence of

enlargement of the aorta believed to be due to pinta has been reported but the occurrence of such lesions has not been definitely established

Prognosis Pinta rarely causes disabling illness or death Aside from the mild symptoms of a chronic infection the disfigurement due to the dyschromic and achromic lesions with accompanying abnormal psychic reactions is the most serious feature of the disease The results of penicillin therapy are excellent

Treatment Penicillin is specific In a series of 700 cases Marquez and his associates observed a dramatic response to one intramuscular injection of 1 200 000 units (4 ml) of penicillin in 2 per cent aluminum monostearate and oil Other long lasting penicillin preparations (in Treatment of Early Syphilis) may be used in the same dosage Both early papular and late pigmented lesions healed promptly and even the vitiligoid spots if present less than five years often regained pigment After one year serological tests were negative in about half the patients When practicable a second injection of the same amount of penicillin should be given one week after the first injection

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Relapsing Fever

(*Recurrent Fever Famine Fever Tick Fever Mianeh Fever Carapata Disease Kimputu*)

Definition Relapsing fever is an acute infectious disease caused by one or another closely related species of spirochetes belonging to the genus Borrelia The disease is characterized by febrile episodes which tend to subside spontaneously and then recur over a period of weeks Epidemiologically two large groups are recognized the louse borne which often occurs in large epidemics and the tick borne relapsing fevers which usually follow an endemic pattern The clinical characteristics of the two tend to be similar

History The first clinical description of the disease was made by Rutty in 1739 Henderson in 1843 described an epidemic in Edinburgh and differentiated the disease from typhus fever In 1868 Obermeier discovered the causative spirochete in the blood of relapsing fever patients and was among the first to associate a particular disease with a specific microbial agent This observation was confirmed by Munch who in 1874 inoculated himself with blood containing motile relapsing fever spirochetes and subsequently acquired the disease and also by Motschutkoffsky (1876) who proved the infectivity of the spirochete by inoculating the blood of patients into healthy persons

In 1891 Flugge suggested that the human body louse might act as a vector and Mackie (1907) in India reached a similar conclusion This belief was later confirmed by the inoculation into monkeys of crushed lice taken from relapsing fever patients In 1904 Ross and Milne in Uganda showed that the tick fever mentioned by Livingston in 1857 was caused by a spirochete which invaded the peripheral blood stream These observations were confirmed in 1905 in the Congo by Dutton and Todd who reported the mechanism of infection in the tick *Ornithodoros moubata* and the hereditary transmission of the spirochetes through the egg to succeeding generations of ticks

Etiology The spirochete of relapsing fever is classified in the genus Borrelia It is a highly flexible spiral organism varying in length from 8 to 30 μ in thickness from 0 3 to 0 5 μ and with five to ten irregular and loosely wound spirals It is actively motile in the fresh state and stains readily with the ordinary analine dyes

Numerous species of relapsing fever spirochetes have been described but these do not differ morphologically from the type species *B recurrentis* and they all induce essentially the same clinical syndrome in man Among the species identified have been *B recurrentis* *B obermeieri* and *B carteri* which are commonly louse borne and *B duttoni* *B hispanica* *B kochi* *B persica* *B turicatae* *B parkeri* *B hermsi* *B venezuelense* and *B neotropicalis* which are commonly tick borne Differentiation is based largely on the ability of the particular organism to infect a given insect host consistent antigenic differences have not been found among these varieties of organisms and the validity of identifying many of them as separate species is questionable

The organisms remain virulent in serum saline at 4° C for about three weeks and survive for long periods when frozen at —70 C Cultivation on artificial media has been reported but cannot be readily accomplished Borrelia multiply luxuriantly in the

chick embryo Monkeys rats mice and hamsters are readily infected guinea pigs and rabbits are less susceptible It is probable that wild rodents constitute the natural reservoir of infection

Agglutinating immobilizing and bactericidal antibodies are readily demonstrable in the serum of infected persons and may persist for many years On the whole however immunological methods of diagnosis are not very helpful for confusing cross reactions often occur with other organisms Moreover the infecting spirochetes usually show variation in their antigenic structure even during the same attack and the antibody pattern becomes correspondingly complex Some degree of immunity appears to follow a clinical attack but data on this point are inadequate Attempts to immunize animals with killed relapsing fever spirochetes have been unsuccessful

Epidemiology Relapsing fever has been reported from nearly all parts of the world at one time or another Its occurrence is largely dependent upon the presence of effective insect vectors especially the body louse and certain species of ticks and upon the existence of environmental factors that favor contact between vector and man Great epidemics of louse borne relapsing fever have swept through central and southeast Europe North Africa and parts of China during the past few decades often occurring concurrently with typhus fever Tick borne relapsing fever is endemic in many parts of the world in the United States sporadic cases have been observed in several of the western and west-central states

Transmission Relapsing fever can be transferred by the inoculation of blood from an infected person but under natural conditions the disease is transmitted by blood sucking arthropods especially lice and ticks although fleas and bedbugs have also been incriminated as vectors

In lice ingested spirochetes quickly enter the hemocele and become abundant from the fourth day infective spirochetes persist for weeks and probably for the rest of the louse s life There is no transovarian transmission The disease is probably transmitted to man not by the bite of the louse but by crushing it infection occurring through the skin or by way of the hands to the conjunctiva

Tick borne relapsing fevers are transmitted principally by the genus Ornithodoros and a score of species have been incriminated as vectors Ingested spirochetes quickly disappear from the digestive tract of the tick but reappear within several days in the malpighian tubules coxal glands salivary glands and legs Human infection probably occurs both through the bite of the tick and by contamination of the human skin with fecal fluid of the tick Spirochetes are transmitted from adult female ticks through the eggs to their offspring for at least several generations

Pathology Relapsing fever spirochetes are found in the peripheral blood during the acute attacks but suddenly disappear just prior to the crisis On the basis of animal experiments it seems likely that spirochetes are present in the internal organs particularly the spleen and brain during periods of remission and it is these sites in which Borrelia can usually be demonstrated at autopsy in man The histopathological changes are not diagnostic The crisis remission and subsequent relapse are reflections of a host parasite interplay in which the development of antibody to the spirochete persistence and later multiplication of antigenic variants of the original strain and the development of new specific antibodies proceed in a cyclic manner It appears likely that death is caused more frequently by complicating conditions and infections than by relapsing fever *per se* but specific deaths may be due to hemorrhagic cerebral lesions meningitis hepatitis or rupture of the spleen

Clinical Manifestations There is considerable variation in symptoms from one outbreak to another and in different patients in the same outbreak No symptom-complex is uniquely associated with a particular species of relapsing fever spirochete or with the mode of transmission

The *incubation period* usually varies from two to fifteen days the average being about seven days

The initial attack which may last two to eight days commonly starts abruptly with chilliness or a chill followed by high fever intense headache pains in the muscles and joints often nausea and vomiting photophobia bronchitis with a troublesome cough and sometimes epistaxis The temperature rises quickly to 104 or 105 F (40 to 40 5° C) and except for slight morning remissions it remains elevated throughout the initial febrile period at the end of which it falls by crisis The pulse is usually rapid 120 to 140 beats per minute during the febrile period Sweating may be profuse during the first day but thereafter the skin is usually

hot and dry and the face flushed Jaundice may occur but is more likely to appear later An erythematous rash is common during this period and later rose colored spots may appear on the trunk and limbs Petechiae may occur which resemble those of typhus fever or early hemorrhagic smallpox Labial herpes is not uncommon

In severe cases neurological and psychic disturbances similar to those occurring in typhus fever *are observed Intense* headache delirium—especially accompanying high fever—and hyperesthesias of the taste and tactile senses may occur Rarely hemiplegia aphasia or symptoms resembling encephalitis or meningitis are observed In such cases there is commonly an increase in lymphocytes in the cerebrospinal fluid in which spirochetes may be demonstrated

In addition to severe myalgia and arthralgia abdominal pain with or without nausea and vomiting may be a prominent feature and gastric hemorrhages have been reported The liver and spleen are usually enlarged and tender

During the acute febrile periods there is a polymorphonuclear leukocytosis of *15 000 to 20 000* per cu mm and the Arneth count is shifted to the left In about 20 per cent of cases serological tests for syphilis are positive and the Weil Felix test may be positive in titers of 1 80 or higher The spirochetes of relapsing fever are commonly demonstrable in the blood during the febrile periods and have also been demonstrated in the urine and *prostatic fluid Albuminuria is common* during the acute attacks Casts and erythrocytes are less frequently observed

The initial attack usually ends by crisis accompanied by profuse sweating and a rapid fall in temperature to normal or below In elderly or weak patients a dangerous state of collapse may occur Diarrhea at this time is not uncommon

The *period of remission* which follows the initial attack lasts three to ten days The temperature remains normal Although prostration is great at first the appetite and strength soon return and the patient may consider *himself completely recovered* Spirochetes can no longer be found in the peripheral blood

A *relapse* follows this symptomless interval in most untreated *cases It is* characterized by a repetition of the more important symptoms of the initial attack except that as a rule they are milder Focal lesions such as jaundice conjunctivitis iritis *transient* cranial nerve abnormalities and uterine hemorrhages are more *common The relapse seldom lasts* as long as the first attack and it also ends by crisis

Additional relapses may occur but are less common When they occur they are usually shorter and milder than the previous febrile periods As many as eleven relapses over a period of four months have been recorded In many cases convalescence is protracted and there may be various sequelae *including iritis otitis* parotitis adenitis neuritis arthritis nephritis and pneumonitis

Diagnosis The final diagnosis of relapsing fever except in epidemic periods rests upon the demonstration of Borrelia in the peripheral blood serological tests are unreliable because of confusing cross reactions Spirochetes which are more numerous early than *late in the febrile attack* can be demonstrated in the blood in wet films preferably by darkfield illumination but may be seen under the light microscope They may also be demonstrated in films stained with Wright or Giemsa stains and when these methods fail by inoculation of rats or mice Inoculation is made intraperitoneally with 0 2 to 0 5 ml of whole or citrated *blood* and *the animal s blood is* examined from the second to seventh day for the presence of Borrelia

The relapsing fevers may be confused with various other acute infections including malaria dengue typhus influenza leptospirosis and early smallpox Clinical differences frequently emerge as the acute attack progresses but definitive diagnosis *depends upon the demonstration* of spirochetes in the blood

Prognosis Relapsing fever in untreated patients may last for three to twelve weeks Case fatality rates vary from 2 to 8 per cent being highest among the malnourished and aged With specific and good supportive treatment the acute attack is cut short relapses are largely eliminated and recovery is rapid

Treatment Supportive treatment in the form of bed rest ample fluids and a soft or liquid diet should be given The arsenicals particularly the neoarsphenamines *which previously were the specific* treatment of choice have been superseded by various other antimicrobial drugs principally penicillin and the tetracyclines

Crystalline penicillin should be given in aqueous solution every *three hours for at* least five days in a total dose of 1 000 000 units per day Failures have been attributed to inadequate dosage

The treatment of choice is chlortetra

cycline in doses of 0 5 gm every six hours for five days then 1 0 gm twice daily for another five days Children under ten years of age should be given half of these doses Oxytetracycline in approximately the same dosage as chlortetracycline seems to be equally effective on the basis of more limited trials chloramphenicol in doses of 250 to 500 mg at three hour intervals for a total of four doses has also been found to be effective With all of these drugs an initial Herxheimer like reaction may occur with marked exacerbation of symptoms

Prevention Since transmission of the disease in nature occurs only through arthropod vectors preventive measures should be directed toward protection against these insects No effective vaccine is available and chemoprophylactic measures are not practicable The louse borne disease can be prevented by taking all of the precautions necessary to avoid exposure to body lice or head lice These measures include the maintenance of good personal hygiene and cleanliness and the disinfestation of louse infested persons and clothing During World War II 10 per cent DDT powder was highly effective in controlling louse infestation but DDT resistant strains of lice have subsequently developed in many areas so that this form of control is now less dependable

The tick borne infections are more difficult to control since these arthropods do not live on the victim As a rule they live in the floors or walls of native houses in the earth of old camp sites in cracks in the floors and walls of caves and in the burrows of various small animals Infested places should not be selected as camp sites and care should be taken to avoid exposure to ticks which usually come out of their hiding places at night and feed on their hosts

Some success in tick control within houses has been reported through the use of an aqueous suspension of benzene hexa chloride in a dose of 15 mg of active substance per square foot of floor treated Two applications are made at four to six week intervals

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Tropical Ulcer

Acute and chronic ulcerative processes usually involving the foot or the lower third of the leg are common in rural tropical areas and in many localities constitute the most common single condition encountered in both outpatient clinic and hospital practice A number of different clinical types can be recognized some constituting clear etiological entities as for example yaws leprosy diphtheria and varicose ulcers to mention only a few

There is however a common type of acute phagedenic ulcer the clinical appearance and evolution of which are sufficiently characteristic to warrant its classification as a distinct clinical entity under the name of Tropical Ulcer It occurs much more frequently in children and adults under thirty years of age than in older persons and is more common in males than in females It affects enormous numbers of people causing massive suffering and economic loss

The etiology of tropical ulcer remains in dispute Trauma often minor appears to play an important role in its inception Spiral organisms belonging to the genus Borrelia and perhaps closely related to *B vincenti* together with *Bacillus fusiformis* are found in a majority of recently developed ulcers but whether these organisms are the primary inciting cause or secondary invaders has not been determined There is impressive clinical and epidemiological evidence suggesting that a dietary protein deficiency particularly in the vitamin A complex is an essential predisposing factor From tropical ulcers of a week s duration or longer many varieties of micro organisms can be cultivated commonest among which are proteus bacilli staphylococci and beta hemolytic streptococci

Clinically tropical ulcer is characterized by rapid destruction of tissue as though

some autolytic agent were present Beginning as a small abraded or ulcerated area 0 5 to 1 0 cm in diameter within twenty four hours there may be a deep circular ulcer with undermined edges measuring 2 0 to 5 0 cm in diameter The margins are not indurated or greatly swollen and the base tends to bleed easily when probed Pain is usually less than the destruction of tissue would portend There is often a foul odor The stage of rapid progression usually terminates within two to five days but the ulcer may persist for months and at times may extend more slowly to involve underlying bone or adjacent areas of skin and subcutaneous tissue

Whatever the initial infecting agent may be continued progression or persistence of the lesion seems clearly to be due in most instances to bacteria which are susceptible to the broad spectrum antimicrobial drugs Treatment with penicillin tetracycline and oxytetracycline has been reported to be effective especially in the early stages before the wide destruction of dermal tissues Penicillin should be administered in a long lasting preparation 1 200 000 units intramuscularly for adults and 600 000 units for children under ten years of age One injection is usually sufficient Tetracycline and oxytetracycline have been used successfully in doses of 1 0 to 1 5 gm daily for four to seven days Antimicrobial therapy should be accompanied by local cleansing of the lesion and by increase in dietary proteins Skin grafting is often necessary in large ulcers and in certain areas itinerant skin grafting teams have been organized for this service Preventive measures include health education directed to the correction of protein deficiency and to the hygienic care of minor injuries of the lower extremities protective clothing to prevent minor injuries and insect bites especially in troops and prompt antimicrobial treatment of developing ulcers

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Rat Bite Fever

Two etiological and clinical entities are included in the medical literature under the term rat bite fever the only important factor common to both being the usual mode of transmission to man indicated by the name The two diseases will be designated respectively *spirillary rat bite fever* and *streptobacillary fever* in accordance with the nature of the etiological agent of each (Watkins)

History Transmission of a febrile disease to man by the bite of a rat has been known for centuries The first clinical description of the disease was by Wilcox in 1840 and a monograph by Miyaka in 1900 awakened interest in the disease In 1914 Schottmuller isolated a streptobacillus from a case of rat bite fever and in 1916 Futaki and his associates demonstrated a spirillum Cases have been reported from many parts of the world Watkins collected 184 cases reported in the United States up to 1946 of these a streptobacillus was demonstrated in 39 and a spirillum in 41 Since 1946 most of the cases reported have been of the streptobacillary type No case has been reported in which both etiological agents were demonstrated to be present simultaneously although such cases may plausibly occur

SPIRILLARY RAT BITE FEVER

(Sodoku)

Definition The disease caused by *Spirillum minus* is characterized by an indurated ulcer at the site of inoculation regional lymphadenitis relapsing type of fever skin rash and often false positive serological tests for syphilis

Etiology Of thirty nine proved cases recorded by Watkins thirty seven followed the bite of a rat one the bite of a weasel and one simple trauma with no known animal contact This is in contrast to Weil's disease which is rarely transmitted by actual rat bite The source of the spirilla at the time of rat bite is believed to be the eye discharge produced by keratoconjunctivitis of the infected rat this discharge in which spirilla have been demonstrated drains into the oral cavity of the rat

Spirillum minus is a short thick spiral organism 2 to 5 μ in length with one to three angular curves and polar flagellae It moves with a rapid darting motion which can best be seen by darkfield microscopic examination It cannot be cultivated in artificial media but upon intraperitoneal inoculation of laboratory animals (guinea pigs rats mice) blood stream invasion and peritoneal involvement occurs In guinea pigs intradermal inoculation often gives rise to a local lesion in which the spirillum can be demonstrated

Clinical Manifestations Unless complicated by secondary infection the rat bite wound heals promptly After an incubation period of five to twenty-eight days there is sudden onset with flare up of the rat bite wound regional lymphangitis and lymphadenitis chills fever malaise and head ache

The site of inoculation becomes swollen indurated painful with an angry purplish hue and may subsequently ulcerate After several days both local and generalized symptoms subside only to reappear again in a few days Periods of fever may then alternate with afebrile periods the temperature rising abruptly and remaining elevated for twenty four to forty eight hours then falling rapidly to normal

This relapsing type of fever is typical and may continue for weeks in untreated cases The first few relapses are usually accompanied by an exacerbation of the inflammation in the wound and the appearance of a rash The eruption is of a dusky red macular or maculopapular character and is sparsely distributed over the trunk and extremities The spleen is often palpable Arthritis is not a common or prominent symptom in contrast to streptobacillary fever although arthralgia and muscle pains may occur A leukocytosis is often but not invariably present and may reach 20 000 or more per cu mm False positive serological tests for syphilis occur in a high proportion of cases The fatality rate as recorded has been about 10 per cent but this should be reduced by modern therapy

Diagnosis Confirmation of the diagnosis is made by demonstration of *Spirillum minus* Exudates from the local lesion and material aspirated from the enlarged regional lymph node should be examined by darkfield microscopy and inoculated into the scrotal skin of guinea pigs or intraperitoneally in mice Darkfield examination of blood is unrewarding but freshly drawn blood plasma should be inoculated intraperitoneally in guinea pigs and mice Spirilla may be demonstrated by darkfield examination of the animal s blood and peritoneal exudates five to fourteen days after inoculation As both mice and guinea pigs occasionally carry spirilla as a natural infection an effort should be made to demonstrate the organism in more than one inoculated animal

Treatment In the pre antibiotic era the response to the arsenical drugs such as neoarsphenamine was usually prompt Antibiotics are now the drugs of choice penicillin streptomycin and the tetracyclines all apparently having therapeutic activity Crystalline penicillin in doses of 30 000 to 40 000 units every six hours for seven days has proved to be satisfactory Penicillin in aluminum monostearate or other long lasting penicillin preparations administered intramusculary in a single dose of 1 200 000 units should also be effective Streptomycin in doses of 0 5 gm for adults and 0 25 gm to 0 1 gm for children given twice daily for three to four days has also been shown to be effective

Chlortetracycline and oxytetracycline in an initial dose of 10 mg per kg of body weight with daily maintenance doses of 30 mg per kg given orally has been recommended

STREPTOBACILLARY FEVER

(*Haverhill Fever Erythema Arthriticum Epidemicum*)

Definition Streptobacillary fever is an acute infection acquired often but not exclusively by rat bite and characterized by acute onset intermittent fever erythematous rash and polyarthritis

Etiology *Streptobacillus moniliformis* is a gram negative pleomorphic organism 2 to 15 μ in length which grows in chains interspersed with swollen bodies among the bacillary forms It is a common inhabitant of the nasopharynx of wild and laboratory rats and most cases of this disease have followed the bite of a rat However one epidemic originally described as Haverhill fever (Place and Sutton) was milk borne and there have been a number of sporadic cases reported in which no direct contact with rats could be established

Clinical Manifestations The incubation period is usually one to five days thus tending to be shorter than in spirillary rat bite fever If the disease follows rat bite the local wound ordinarily heals without incident but occasionally an abscess develops in the wound Regional lymphadenitis is not a prominent feature The onset of the disease is abrupt with chills fever vomiting headache and rather severe pains in the back and joints A maculopapular rash develops early usually within the first forty-eight hours and at this stage the disease is dengue like in its manifestation Often there is a remission of the fever after forty eight to seventy two hours Within the first five days however one or more joints usually become swollen red and painful with recurrence of the septic type of fever The acute arthritis is one of the most prominent and persistent symptoms in streptobacillary fever Subcutaneous

abscesses from which the infecting organism has been recovered have been observed Bronchopneumonia also occurs in a small proportion of cases There is a leukocytosis of 10 000 to 20 000 cells per cu mm with a relative increase in neutrophils False positive serological tests for syphilis occur *only rarely in contrast to spirillary rat bite fever*

Relapse is rare but in the absence of specific therapy convalescence may be prolonged because of the affected joints About 7 per cent of reported cases have been fatal but this proportion can probably be substantially reduced by modern therapy Ulcerative endocarditis and myocardial abscesses have been found post mortem

Diagnosis Even without a history of rat bite an acute febrile illness accompanied by nonmigratory polyarthritis and skin rash is highly suggestive of streptobacillary fever Serum agglutinins for *Streptobacillus moniliformis* develop within ten days and reach a maximum in three to four weeks An agglutination titer of 1 80 or higher is regarded as diagnostic demonstration of a four fold or greater rise in titer is especially significant *Streptobacillus moniliformis may be recovered from the patient s blood* or more readily from fluid aspirated from an affected joint or abscess Isolation is accomplished by implantation in special media containing serum or ascitic fluid or by intraperitoneal inoculation of mice Infection is usually fatal to mice in six to twelve days and the organism can in turn be demonstrated in their blood In liquid or semisolid media colonies develop well below the surface of the medium and have a characteristic fluffy cotton ball appearance Mice which survive the infection frequently develop joint lesions from which the organism can be isolated

Treatment Penicillin appears to be specific for this disease although relatively few cases have been reported since this *drug* has been available In the absence of more definitive information large doses of penicillin 1 200 000 units per day of the aqueous form for adults and older children and one half this amount for young children should be given daily for at least seven days Further experience may show smaller doses to be effective

Streptomycin in a dose of 1 0 to 2 0 gm daily until the patient has been asymptomatic for two to three days has also been found to be effective No data are available on the efficacy of the other antimicrobial drugs In contrast to spirillary rat bite fever the arsenical drugs *are not effective in the* streptobacillary disease

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The Leptospiroses

Definition The leptospiral infections of man comprise a group of syndromes including Weil s disease pretibial fever meningitis *nephritis arthritis iridocyclitis* and a mild grippe like illness

More than twenty different strains of leptospirae have been recognized by serological methods The strains known to be associated *with human infection in the United* States include *L icterohemorrhagiae L canicola L pomona L autumnalis* and *L grippotyphosa*

Epidemiology A variety of wild and domestic animals including rats mice dogs cattle and swine may become infected by leptospirae and the infection is usually chronic characterized by excretion of living organisms in the urine for long periods of time Humans may become infected by contact with materials contaminated by such urine for this reason certain occupations carry a special hazard of leptospiral infection These include sewer work *ditch* digging fish cutting farming and slaughterhouse work Infection has also been ac*quired from swimming in pools* of contaminated water

Pathogenesis and Pathology The portal of entry is believed to be either the respiratory or the gastrointestinal tract although conceivably leptospirae can gain access through cuts or abrasions of the skin Once the organisms have penetrated the mucosal *or* skin barrier the type of clinical disease produced will depend upon the strain of in

fecting organism as well as upon the host s response In young persons the *mild grippe lil e* and *meningeal* forms of disease are more likely to develop whereas in persons past the age of thirty the more severe *Weil s disease* is commonest This form is most frequently associated with infection by *L icterohemorrhagiae* although it is occasionally produced by *L canicola*

Presumably in all forms of infection there is an initial leptospiremia This can be demonstrated in the great majority of cases of Weil s disease any time during the first three to five days of illness Circulating antibodies usually make their appearance during the second week of illness and organisms can seldom be demonstrated in the blood after that time Leptospirae may appear transiently in the urine during the latter part of the second or the third week A chronic urinary carrier state does not become established in the human as it so frequently does in animals

The cellular response to acute inflammation produced by leptospirae varies The muscle lesions of Weil s disease are principally those of acute localized degenerative changes in muscle fibers with little inflammatory reaction about them In the liver the microscopic evidence of disease is often surprisingly meager even in deeply jaundiced patients There may be minimal evidences of cytoplasmic degeneration some active hepatocellular regeneration and bile stasis In the most severe cases areas of focal necrosis may be observed In the kidney the pathological changes may be more obvious here one finds degeneration and necrosis of convoluted tubules diffuse interstitial inflammation and numerous granular casts and cellular debris in the collecting tubules The cellular response in meningitis is principally lymphocytic The circulating leukocytes of the blood vary in number according to the disease picture in the grippe like meningeal and pretibial fever syndromes the leukocyte count is usually in the normal range whereas in Weil s disease a well marked leukocytosis is the usual finding

WEIL S DISEASE

Clinical Manifestations The incubation period is usually eight to twelve days The onset is abrupt often with one or more chills followed by fever varying from 102° to 104 F Headache and photophobia are prominent symptoms and the patient complains of severe muscular pains in the lumbar region and calves There may be nausea vomiting or diarrhea Sore throat and cough are less common The conjunctivas are conspicuously injected Herpes simplex may develop about the mouth The spleen seldom becomes palpably enlarged

Fever usually lasts four to seven days then terminates by rapid lysis There may however be no real improvement in the clinical state since it is at about the fifth or sixth day that hepatitis and nephritis are likely to become obvious About 60 to 70 per cent of cases recognized as having Weil s disease show *hepatitis* with icterus and enlarged tender liver Jaundice deepens during the next few days then usually begins to subside by the twelfth or fourteenth day In cases terminating fatally there may be increasing cholemia until death *Nephritis* is somewhat less frequent being evident in less than half of the recognized cases It is manifested by albuminuria and hematuria and in severest cases by oliguria and azotemia Renal involvement is rare without evidence of liver disease In about 10 per cent of cases there is clinical evidence of meningeal inflammation *i e* pain and stiffness of the neck with Kernig s and Brudzinski s signs Other unusual manifestations include *petechial and purpuric lesions* of the skin and *iridocyclitis* or *optic neuritis*

Relapse with fever and muscle pain occurs in about 20 per cent of all cases during the third or fourth week The symptoms are usually milder than in the original attack

Diagnosis Leptospirae have been identified in the blood by darkfield microscopy during the first five to seven days of illness This procedure is reliable only in the hands of an experienced observer since it is easy to mistake strands of fibrin moved about by brownian motion for leptospirae A preferable procedure is to inoculate young guinea pigs intraperitoneally with the patient s blood These animals show signs of infection (fever and jaundice) three to fifteen days later and the organisms can be recovered from their tissues After the first week of illness it is rarely possible to demonstrate leptospirae in the blood but during the second or third week they may be recovered from the urine by animal inoculation in perhaps 20 per cent of cases Occasionally leptospirae can be recovered from the blood or urine of human beings by cultural methods

Antibodies usually appear in the blood during the second week of illness and reach peak levels by the third or fourth week Agglutinin titers of 10 000 to 100 000 are not uncommon For best results the antigen

abscesses from which the infecting organism has been recovered have been observed Bronchopneumonia also occurs in a small proportion of cases There is a leukocytosis of 10 000 to 20 000 cells per cu mm with a relative increase in neutrophils False positive serological tests for syphilis occur only rarely in contrast to spirillary rat bite fever

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only on the anterior aspects of the legs (hence the name "pretibial") but is occasionally generalized even to the face. The lesions consist of irregular slightly raised areas of erythema varying in size and shape occasionally being 5 cm in diameter.

The course of illness is brief, fever subsiding in four to eight days, and there are no residual defects.

The distinctive laboratory finding is leukopenia in the early stages with return to normal levels in convalescence.

Definitive diagnosis can be made by isolating *L. autumnalis* from the blood during the early stage of illness or by demonstrating the appearance of specific antibodies for that organism during convalescence.

LEPTOSPIRAL MENINGITIS
(*Swineherd's Disease*)

This form of leptospirosis is most commonly observed in young persons and there is a peak incidence in the latter part of the summer. It was first described in Europe where it was called swineherd's disease. For a time it was thought to be due to a virus similar to that of lymphocytic choriomeningitis, but the leptospiral etiology has since been established beyond doubt. Cases have been shown to be caused by *L. icterohemorrhagiae*, *L. canicola* and *L. pomona*. The clinical picture is indistinguishable from that of other nonpurulent meningitides caused by viruses such as lymphocytic choriomeningitis, mumps and nonparalytic poliomyelitis. There is usually an abrupt onset of illness with headache, fever, pains in the muscles, some stiffness of the back and neck. The temperature may go as high as 103 or 104 F. The cerebrospinal fluid may be normal during the first two or three days, later a mononuclear pleocytosis develops, the cell count usually being between 50 and 300 with occasionally as many as 50 per cent being polymorphonuclears. Dextrose content of the cerebrospinal fluid is normal and the protein is moderately elevated, usually being 50 to 100 mg per 100 ml. The peripheral leukocyte count is normal. Symptoms of headache and malaise persist for two to ten days, then subside and complete recovery ensues. Diagnosis can be made only by isolation of leptospirae from the blood or cerebrospinal fluid or by serological tests.

GRIPPE-LIKE ILLNESS AND OTHER FORMS OF LEPTOSPIRAL INFECTION

Grippe-like Illness. In many parts of the world leptospiral infection is commonly observed in the form of a brief febrile disease without localizing manifestations pointing either to hepatic or to meningeal involvement. These infections are usually caused by strains of leptospirae other than *L. icterohemorrhagiae*, such as *L. canicola*, *L. pomona* and *L. grippotyphosa*. According to the occupational factors these diseases are designated variously as *rice field fever*, *mud fever*, *cane fever* and so forth. There are no distinctive manifestations and diagnosis can be made only by demonstration of the agent in the blood or urine or by serological methods. In a case recently reported from Tennessee, in addition to the above symptoms of fever and malaise there was an acute polyarthritis with a clinical picture somewhat suggestive of acute rheumatic fever.

Iridocyclitis. Acute inflammation of the iris and uveal tract may occur as a late complication of Weil's disease, usually coming on in the third or fourth week, but sometimes as an isolated entity several months after recovery from generalized leptospiral infection. Such cases may come under the care of ophthalmologists, and the relationship to the preceding leptospiral infection may not be recognized because of the long latent period which has occurred. The outcome is usually satisfactory with subsidence after two or three weeks, leaving no permanent damage to the eye.

Nephritis. In rare instances leptospiral infection is principally manifested by involvement of the kidney with hematuria, proteinuria, cylindruria and oliguria. Such a picture can be easily be confused with that of acute glomerulonephritis. The eventual outcome is complete recovery.

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should be freshly prepared from cultures

In the *blood* a polymorphonuclear *leukocytosis* from 10 000 to 30 000 per cu mm is the rule This is of considerable value in differential diagnosis There may be a moderate reduction in blood *platelets* although not usually sufficient to account for the hemorrhagic tendency sometimes manifested Examination of the *cerebrospinal fluid* is a useful guide to diagnosis of Weil s disease In 80 to 90 per cent of all cases regardless of the presence of clinical signs of meningitis there is a pleocytosis varying from 10 to several hundred cells per cu mm the majority being lymphocytes In patients with jaundice the cerebrospinal fluid also becomes xanthochromic The *urine* may show no abnormality during the first few days but with the development of hepatitis bilirubin may appear Nephritis is evidenced by hematuria cylindruria and proteinuria

Muscle biopsy can also provide an early presumptive diagnosis of Weil s disease for the tissue obtained may reveal a characteristic picture consisting of areas of focal necrosis in a segment of muscle fiber with little vascular change or infiltration by inflammatory cells

Differential Diagnosis During the first few days of illness the picture is that of an acute systemic infectious disease which can hardly be differentiated from a variety of other processes including acute pyogenic infections influenza and typhus fever Severe muscle pain suffusion of the conjunctivas leukocytosis and pleocytosis in the cerebrospinal fluid are features which should suggest leptospiral infection After the first week there may be little or no fever but jaundice is likely to appear At this stage the principal problem is differentiation from viral hepatitis Again the presence of conjunctival suffusion leukocytosis and cerebrospinal fluid abnormalities are helpful In acute hemolytic jaundice reticulocytosis is likely to be present and bile may not be found in the urine

Prognosis The fatality rate is approximately 5 per cent in recognized cases of Weil s disease As many mild forms of the disease probably go unrecognized the actual death rate is doubtless considerably lower The prognosis is grave if there is severe hepatic and renal involvement with deep jaundice azotemia oliguria or circulatory impairment

Treatment General supportive measures to be used in acutely ill patients are the same as for any acute infectious disease

It has been difficult to evaluate different kinds of specific therapy in Weil s disease because of its variable severity and natural early subsidence of fever In view of good results in the treatment of experimental infection with antiserum a few attempts have been made in humans to give serum therapy or transfusions of blood from patients who have recovered from the infection The results have not been clear-cut and neither procedure has been widely accepted

Penicillin is effective in therapy of experimental infections if given early in the course of the disease but not after the infection has become well established The drug has been administered more or less routinely to patients with Weil s disease since 1944 but its value still remains questionable Deaths have occurred despite administration of moderately large doses of the drug The tetracyclines and chloramphenicol are also effective in experimental infections but their usefulness in treatment of human disease has not been clearly demonstrated In a study of various antimicrobial drugs alone and in combination carried out in Puerto Rico there was no definite benefit demonstrable with any

PRETIBIAL FEVER
(*Fort Bragg Fever*)

An acute infectious disease which was observed among soldiers stationed at Ft Bragg North Carolina during the period 1942–1944 was given the names pretibial fever and Fort Bragg fever An agent probably responsible for the disease was isolated from the blood of a patient in 1944 and maintained by animal passage in laboratories for some years thereafter Originally assumed to be a filterable virus this agent was shown in 1952 by Gochenour and associates to be *L autumnalis* The serum saved from patients convalescent from pretibial fever was found to contain specific agglutinins for this agent Sporadic cases of the syndrome are still observed occasionally in North Carolina and in Georgia and it is to be presumed that the disease still occurs in those regions

The *clinical manifestations* are those of an acute self limited exanthematous infectious disease There is an abrupt onset with chilliness or chills malaise headache and photophobia Some patients have cough and coryza some have nausea and vomiting On examination the distinctive physical findings are splenomegaly and a cutaneous eruption The rash appears about the fourth day of illness It is most often located

only on the anterior aspects of the legs (hence the name pretibial) but is occasionally generalized even to the face The lesions consist of irregular slightly raised areas of erythema varying in size and shape occasionally being 5 cm in diameter

The course of illness is brief fever subsiding in four to eight days and there are no residual defects

The distinctive laboratory finding is leukopenia in the early stages with return to normal levels in convalescence

Definitive diagnosis can be made by isolating *L autumnalis* from the blood during the early stage of illness or by demonstrating the appearance of specific antibodies for that organism during convalescence

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PROTOZOAN INFECTIONS

Amebiasis

Definition Amebiasis is the disease caused by infection with the protozoan *Endamoeba histolytica* It affects the colon primarily and other organs secondarily especially the liver Amebiasis is characterized by gastrointestinal and constitutional symptoms and almost always runs a chronic course which is subject to acute exacerbations The term *amebic dysentery* is properly applied only to the severe cases in which there is diarrhea with blood and mucus in the stools The term *acute amebic dysentery* is often applied to the acute exacerbations but truly acute cases are probably rare They are the result of heavy infections such as may occur in epidemics due to contamination of water supplies with sewage

Etiology and Pathogenesis The parasite has two phases trophozoite and cyst The active trophozoites which are present in infected tissues cause the pathological changes and the cysts which develop from trophozoites on the surface of the mucosa of the colon are responsible for the transmission of the disease The trophozoites are 10 to 40 μ in diameter They exhibit progressive flowing motility and have a nucleus with uniform distribution of peripheral chromatin and a delicate usually centrally placed nucleolus Some show ingested erythrocytes Cysts are from 5 to 20 μ in diameter and contain one to four nuclei similar to those of the trophozoites as well as chromatoid bodies with blunt rounded ends They have a well-defined wall and are resistant to freezing and partial drying but not to boiling or complete drying

When cysts are swallowed they pass to the cecum There by a process called excystation several trophozoites emerge from each cyst and attack and invade the tissues of the colon The presence of the intestinal bacteria is essential to the production of the intestinal lesions

Incidence and Epidemiology Amebiasis is by no means limited to the tropics but is world wide in distribution and is found as far north as the Arctic Circle Amebiasis is more prevalent and more severe in the tropics however it may produce severe and even fatal illness in persons who have lived only in the temperate zones It is more prevalent in areas where sanitation is poor In areas devoid of any sanitary facilities rates of infection are often more than 50 per cent In the United States as a whole Craig has estimated that 10 per cent of the population is infected

Amebiasis may occur at any age In unsanitary areas children tend to show the same rates as adults once they have passed the age of five years In areas of good sanitation children show a much lower incidence than adults Infection rates are little influenced by sex but 85 to 90 per cent of amebic liver abscesses occur in adult males Children rarely develop this complication

Infection takes place when the cysts are ingested This usually results from fecal contamination of food or drink Water is contaminated by sewage Food may be contaminated by being fertilized with human excreta by flies exposed previously to infected excrement or by food handlers who are careless in their habits The last method is responsible for the endemicity of amebiasis in places with well protected water and food supplies Children may infect themselves when playing in soil contaminated with feces Infection by close personal contact occurs in institutions for mental illness when fecal contamination of the environment plus uncontrollable personal habits are combined

Epidemics of amebiasis occur occasionally Perhaps the most famous is that which occurred in Chicago in 1933 when there were more than 1400 cases and more than 100 deaths Epidemics are usually the result of direct contamination of the water supply with sewage due to faulty plumbing

Morbid Anatomy Amebiasis is characterized by ulceration of the colon which varies greatly in extent and intensity In fatal cases ulcers may be present throughout the colon and occasionally extend to the terminal ileum When the process is focal the lesions are most often concentrated in the cecum and ascending colon The second most frequent localization is in the rectosigmoid area The larger ulcers penetrate to the submucosa and extend laterally assuming a flask shape Liver abscess results from the coalescence of focal areas of necrosis The contents are typically reddish brown in color and the wall is ragged The affected tissues usually show little cellular reaction in amebiasis

Clinical Manifestations The symptoms of amebiasis vary greatly from patient to patient both with respect to severity and to the presence or absence of specific complaints They may also vary in severity in the same patient and there may be intervals of relatively good health The classic

dysenteric form with cramps diarrhea and bloody mucoid stools is seen in only a small proportion of cases at least in the temperate zones Patients with severe dysentery usually have a history of preceding milder gastrointestinal disturbances although this may be brought out only on careful questioning

Many infected persons have no complaints They may be called "carriers in the sense that they constitute a source of infection for others In the biological sense however the term carrier does not apply since they often have pathological changes in the colon and may develop clinical manifestations including liver abscess at any time Sometimes following treatment the so-called carrier will recognize that he has *really been having symptoms which were* so mild that he was not aware of them The insidious character of mild amebiasis is striking The symptoms are often vague and may be peculiarly described by the patient Consequently a functional disturbance may be suspected especially since the blood count erythrocyte sedimentation rate and other routine studies are usually normal in mild infections Patients with amebiasis are not infrequently treated for spastic colon or referred for psychiatric advice

Diarrhea is a common but by no means constant symptom About one third of patients do not have it The diarrhea may be persistent or intermittent mild or severe In some instances it is so mild that it is not noticed by the patient It may alternate with constipation and in some instances the latter is the more prominent symptom When there is diarrhea stools vary from slightly loose to watery They sometimes contain mucus and less frequently blood Other common gastrointestinal symptoms are abdominal distress distention abdominal pain and tenesmus *Vomiting* is unusual but nausea occurs in some cases *Abdominal pain* may be generalized or localized When it is localized it is often felt in the right lower quadrant owing to involvement of the cecum In such instances appendicitis may be suspected and a normal appendix is sometimes removed before the correct diagnosis is made True amebic appendicitis occurs but it is rare

Constitutional symptoms often accompany the gastrointestinal manifestations and may overshadow them They include undue fatigue fever which is most often not high vague somatic aching backache and arthralgias Rarely actual arthritis suggesting the rheumatoid form is seen There may also be nervousness irritability or dizziness suggesting a neuropsychiatric disorder Weight loss is not characteristic It may occur in relatively severe cases but is rare in mild cases Patients with pronounced diarrhea may maintain a normal weight and are sometimes actually obese Anemia is rare in mild cases but frequent when manifestations are severe

Patients with uncomplicated amebic colitis may have tenderness over the cecum or other portions of the colon Otherwise physical signs are usually absent unless a very severe dysentery occurs In such cases the patient shows varying degrees of emaciation and dehydration

Sigmoidoscopic examination is most often negative in amebiasis In hospital *practice it is not unusual to find ulcerations* or other abnormalities in one third or more of cases in office practice however at least in the temperate zone less than 5 per cent of those infected show visible changes The most typical finding is the presence of ulcers of an irregular shape set in an otherwise normal mucosa In some cases there is a friable hemorrhagic mucosa suggesting nonspecific ulcerative colitis it is probably due to secondary bacterial infection

Roentgenographic examination of the colon is usually negative but in a substantial minority of patients abnormalities are detected Most often these are observed in the cecum which is irregular narrowed and altered in shape due to edema and spasm Spasm may occur in other portions of the colon

Both sigmoidoscopic and roentgenographic examinations are advisable in amebiasis They give some indication as to the extent of the disease may help in evaluating cure and may detect coexisting but unrelated conditions such as neoplastic disease

Complications *Abscess of the liver* is the most common serious complication of amebiasis It may occur in patients with no previous history of intestinal disorder There is usually only one abscess and in a large majority of cases it occurs in the right lobe While the onset of symptoms may be acute it is usually insidious and the diagnosis is frequently difficult The initial symptom may be *unexplained fever* *Pain* over the liver may not occur until several weeks have passed The pain may be felt in the upper abdomen or right lower chest and may be referred to the right shoulder or scapular area Anorexia and weight loss are frequent Nausea may

occur but vomiting is rare The fever is usually moderate in degree it may be associated with sweats

The physical signs depend on the direction in which the liver enlarges When the enlargement is chiefly upward dullness and diminished breath sounds may be noted at the right lung base simulating pneumonia If the enlargement is downward it can be detected by palpation In either case there is tenderness over the liver edge and pain on percussion over the liver area Roentgenographic examination of the chest may show elevation and fixation of the right diaphragm or merely impairment of its excursion In some cases there is a localized bulge in its contour Pleural effusion is present in some instances The blood shows a moderate increase in the leukocyte count most often not exceeding 20 000 per cu mm with a moderate increase in the percentage of neutrophils usually only to 75 or 80 per cent Anemia is frequent Marked leukocytosis and high fever are usually associated either with a perforated abscess or with secondary bacterial infection Perforation is not unusual since the diagnosis may be overlooked for weeks or months Most often the abscess perforates into the subphrenic space right pleural cavity or right lung Less often perforation occurs into other organs adjacent to the liver or into the peritoneal cavity

There may be less profound involvement of the liver with manifestations indicating recurrent *acute hepatitis* or low grade *chronic hepatitis* In these cases jaundice is rare but one or more of the tests of liver function frequently show an abnormal result The liver may or may not be enlarged to palpation Tenderness over the liver is often but not invariably present Symptoms suggesting chronic hepatitis are right upper quadrant pain nausea variable appetite and intolerance to alcoholic beverages

Pulmonary abscess is usually the result of extension from a liver abscess occasionally it occurs independently as an isolated phenomenon Other rare complications are brain abscess and involvement of the skin usually in contiguity with internal infection that is adjacent to the rectum a colostomy or the drainage tract of a liver abscess In the colon major complications are very unusual They include perforation stenosis and a localized productive inflammation called ameboma which produces the clinical manifestations of a *tumor*

Diagnosis Amebiasis should be suspected in patients with ill-defined gastrointestinal complaints as well as those with diarrhea in patients with unexplained constitutional symptoms and in patients with anicteric hepatitis Periodic routine examination of the stools for *E histolytica* is advisable in persons exposed to unsanitary conditions

The diagnosis of intestinal amebiasis is only exceptionally justified without the demonstration of *E histolytica* in the stools The identification of *E histolytica* can be correctly made only by technicians who have had several months of specialized practical training in protozoological diagnosis The parasite is most readily found in diarrheal stools so that if diarrhea is not present it should be produced by the administration of a saline cathartic These diarrheal stools must be examined promptly using warm slides and saline in order that the characteristic motility of the trophozoites may be observed

In diarrheal stools it is usual to find only trophozoites Cysts may occur but are more frequently found in formed stools In many patients cyst formation is a variable process so that for periods as long as several weeks it may be impossible to detect them Hence reliance on casual formed specimens greatly reduces the likelihood of a positive finding

Cultures have only a limited value in the diagnosis of amebiasis for in many cases the amebas do not grow readily In selected cases the method is a useful adjunct to the direct examination of fresh stools Iron hematoxylin stained preparations are useful for permanent records but are too time consuming for routine use

As lesions are frequently present only in the upper colon specimens obtained through the sigmoidoscope are of limited value they are most likely to yield positive results when visible lesions are present Great care must be exercised not to mistake the leukocytes frequently present in mucus for amebas

The administration of antimicrobials such as the sulfonamides or the tetracyclines before the stool specimens are obtained greatly increases the difficulty of finding *E histolytica* Hence the empirical treatment of diarrheas with these agents is not advisable The presence of mineral oil and barium in the intestinal tract temporarily interferes with the detection of amebas

When there are manifestations suggestive of amebic abscess of the liver the demonstration of *E histolytica* in the stools helps to confirm the diagnosis In some

cases it is not possible to find the parasite This is true especially if antimicrobials have been given empirically because the *patient has had an unexplained fever The specific complement fixation reaction* is of considerable value since it appears to be positive in all cases of liver abscess due to *E histolytica* In patients with hepatitis but no abscess the reaction may be either positive or negative The test is negative in the large majority of cases of uncomplicated intestinal amebiasis In cases in which the reaction is positive it may remain so for many months after cure Unfortunately the results reported on a research basis cannot be consistently obtained in the routine diagnostic laboratory probably because of the technical difficulty of *producing a satisfactory antigen*

Further corroborative evidence for the diagnosis of amebic abscess is the response to specific therapy In uncomplicated amebic abscess there is almost always prompt and dramatic abatement of symptoms within twenty four to forty-eight hours after emetine is started The response to chloroquine is less dramatic

Some patients are so seriously ill that there may not be time to carry out proper stool examinations and therapeutic tests In these cases it may be necessary to perform an exploratory laparotomy because the diagnosis is obscure and an acute surgical condition is suspected If in the course of such an operation an abscess of the liver is encountered it should be aspirated and specific therapy for amebiasis instituted immediately pending laboratory examination of the material obtained In the absence of some other obvious infection liver abscess is almost always amebic If the aspirated material is brown in color one can be almost certain of the diagnosis even though it does not usually contain demonstrable *E histolytica* However if open drainage has been instituted and inadvertently no emetine or chloroquine has been given the parasites can sometimes be found in the discharge after several days since the material now comes from the ameba containing abscess wall

The aspirate should be cultured for bacteria A negative result supports the diagnosis of amebic abscess A positive result indicates either secondary infection of such an abscess or a nonamebic abscess

Prognosis Many cases of mild amebic colitis respond rapidly and completely to a single course of an oral amebacide A few prove more resistant In general the more severe the manifestations the more likely the case is to be resistant to cure In acute hepatitis and liver abscess the prognosis as to cure is excellent Low grade hepatitis *often requires prolonged treatment* and may be difficult to clear up permanently and completely Death from amebiasis occurs only when the disease goes unrecognized or occasionally in patients weakened by other illness or subjected to massive amebic infection A fatal outcome is most often due to liver abscess or its complications

In those cases of amebiasis in which cure is not accomplished the patient can be kept in reasonably good health with periodic specific treatment Reasonable criteria of cure are freedom from clinical manifestations for one year together with *postcathartic stool specimens which are* repeatedly negative for *E histolytica* Stool specimens should be examined on approximately six different occasions at increasing intervals over the period of one year following the completion of therapy

Treatment In severe amebic colitis characterized by marked diarrhea usually with blood in the stools and fever treatment should be started with emetine hydrochloride 1 0 mg per kg of body weight (maximum 0 065 gm) administered daily by deep intramuscular injection On the first day it should be divided into two doses so that any idiosyncrasy may be detected The emetine should be continued *only long* enough to control the severe symptoms but not for more than five days in order to avoid serious toxic effects on the heart Emetine should be followed by five days of antibacterial therapy either a combination of sulfasuxidine 1 0 gm four times a day and penicillin 500 000 units intramuscularly once a day or one of the tetracyclines by mouth 0 25 gm four times a day Then di iodohydroxyquinoline (Diodoquin) 0 65 gm four times a day is given for twenty days Finally one to two weeks after termination of this regimen either carbarsone 0 25 gm three times a day for 10 days or fumagillin (Fumidil) 10 mg three times a day for ten days should be prescribed

If the patient has moderate diarrhea and no fever emetine is omitted In mild or asymptomatic amebiasis no antibacterial therapy is necessary and it is usually sufficient to give a single treatment with Diodoquin carbarsone or fumagillin in the doses mentioned above Diodoquin is preferred because of the low incidence of untoward effects none of which is serious Carbarsone often produces gastrointestinal dis

turbances less often skin eruptions and rarely jaundice Fumagillin not infrequently produces marked gastrointestinal irritation it may possibly cause neutropenia

A considerable number of other drugs have been and are used as oral amebacides None has any distinct advantage over those already discussed Some are less effective others are more prone to produce adverse effects In any individual case however a statistically less effective drug may prove effective when a more standard drug has failed The more important alternative amebacides are

(maximum 0 065 gm) once a day for ten days The pulse and blood pressure should be checked before each injection If there is a pronounced fall of blood pressure or rise in pulse rate the treatment should be stopped The patient s activity should be markedly restricted not only during therapy but for four weeks thereafter since emetine is slowly excreted

Specific therapy will cure a majority of patients with liver abscess If there is persistent fever or other evidence of incomplete resolution of the abscess drainage by aspiration or open operation is indicated

Iodine Quinoline Compounds	
Vioform	0 25 gm 3 times a day for 10 days
Chiniofon (Anayodin)	1 0 gm 3 times a day for 10 days
Arsenical	
Milibis (bismuth glycoarsanilate)	0 5 gm 3 times a day for 8 days
Oral Antimicrobials	
Chlortetracycline	0 5 gm 4 times a day for 2 days or more followed by 0 25 gm 4 times a day for the balance of 7 days
Oxytetracycline	0 5 gm 4 times a day for 7 days
Bacitracin	20 000 units 4 times a day for 10 days

Chiniofon was the precursor of Diodoquin it is little used now because it is less effective and frequently causes diarrhea which prevents administration of an adequate dose Vioform even at a dose of 0 5 gm three times a day twice the standard dose is less effective than Diodoquin Milibis is no more effective than carbarsone and has similar drawbacks The tetracyclines probably act indirectly by depressing the intestinal bacteria upon which *E histolytica* depends for some essential factor or factors The tetracyclines are almost as effective as Diodoquin in mild amebiasis but are apt to produce marked gastrointestinal symptoms which may be more troublesome than those of mild amebiasis Bacitracin is less effective than the tetracyclines but is relatively free of side effects

Amebic liver abscess and acute amebic hepatitis are treated with chloroquine (Aralen) diphosphate rather than emetine since adequate doses of the latter may have serious toxic effects on the heart The dose is 0 25 gm three times a day for two weeks Visual disturbances due to chloroquine may be ignored if there is marked nausea or dizziness or severe insomnia the dose is reduced to 0 25 gm twice a day and treatment is prolonged so that the total dose is still 10 to 11 gm If emetine is used because chloroquine has not been effective or cannot be obtained the dose is 1 0 mg per kg of body weight

In *chronic amebic hepatitis* the dose of chloroquine should be 0 25 gm twice a day since these patients seem to tolerate it less well than those with acute involvement A total dose of 10 gm should be used In addition the general measures used in other chronic hepatic disease are indicated All patients with amebic liver disease should be treated for intestinal involvement as well even if there are no symptoms of colitis Neither emetine nor chloroquine can be relied upon to clear up the intestinal infection

Prevention Ordinary concentrations of chlorine including those produced by Halazone tablets cannot be relied upon to kill amebic cysts For small scale use a tablet containing tetraglycine hydroperiodide (Globaline) which liberates iodine is effective against amebic cysts as well as common water borne bacterial infections For public water supplies the addition of proper filtration to chlorination is effective Other preventive measures are sanitary disposal of feces avoidance of use of human excreta for fertilization fly control and detection and treatment of mild or asymptomatic infections especially in food handlers

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Coccidiosis

Etiology Coccidiosis is an infection caused by sporozoan parasites belonging to the genus Isospora Only a few hundred infections of man with Isospora have been reported but the infection is undoubtedly more common in many countries with poor sanitary conditions than published reports would indicate Surveys in Brazil and Egypt demonstrated Isospora oocysts in approximately 0 1 per cent of the stools examined The majority of reported infections have been among British soldiers serving in the Middle East but the infection is world wide Infections originating in Africa China Japan India the Philippines Indonesia Hawaii South America and North America have been reported Magath found only one infection in 60 000 patients examined at the Mayo Clinic Many of these patients were from foreign countries *I bigemina* found commonly in the dog appears to be indistinguishable from *I hominis* and may be a source of human infection

Ingestion of oocysts of species of Eimeria parasitic in the liver of herrings in the testes of sardines and in the liver of rabbits may lead to erroneous diagnosis These "foreign coccidians pass through man s alimentary tract intact and are examples of pseudo parasitism

Morbid Anatomy The life cycle and pathology of Isospora infections in man have been inadequately studied because limited postmortem material has been available The schizogonic phase of the cycle probably occurs in the epithelial cells of the lower portion of the ileum The encysted fertilized eggs (oocysts) pass down the bowel and out in the feces In *I belli* infections oocysts 30 by 12 μ are passed in the feces They are in early stages of development the mature oocyst contains two sporocysts each with its four sporozoites *I hominis* is usually passed fully developed the oocyst wall is usually absent and the sporocysts containing four sporozoites may be single or coupled in pairs each being 15 by 10 μ The sporocyst or oocyst containing two sporocysts with their eight sporozoites are ingested with feces contaminated food or drink hatch in the small intestine and initiate a new infection

Clinical Manifestations Experimental infections in human volunteers have demonstrated the pathogenicity of Isospora Diarrhea begins one week after the ingestion of the oocysts and persists for one to four weeks The stools are liquid brownish yellow in color contain a large amount of undigested material and fat and Charcot Leyden crystals are often present Fever abdominal pain nausea and vomiting of varying degrees accompany the diarrhea Typical oocysts appear in the stool after two to four weeks and persist for approximately a month The eosinophile count was essentially normal in the experimental infections It has been reported to be increased in a number of patients with natural infections in whom however Schistosoma hookworm or *E histolytica* were also present Clinical observation of patients during a period of several months indicates that the infection may be present without the production of significant signs or symptoms Infections with Isospora appear to be self limited and last only a few weeks unless there is repeated oral reinfection In the *treatment* of coccidiosis there is no specific therapy available although a number of compounds have been used with considerable success in the coccidiosis of domestic animals

Prevention The prevention of coccidiosis consists of avoiding water and food which may be contaminated with Isospora oocysts Thorough cooking of food and boiling of water will prevent infections when in endemic areas

HAROLD W BROWN

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Malaria

Definition Malaria is an infectious febrile disease produced by several species of protozoa belonging to the single genus plasmodium It is transmitted naturally from host to host only by the bite of an infected *anopheline mosquito In the mosquito the* development of the parasite is observed on the stomach wall and in the salivary glands while in man it is continued in the erythrocytes Clinically the disease is characterized by paroxysms of severe chills fever and sweating These paroxysms may occur daily (quotidian) on alternate days (tertian) or with an interval of three days between chills (quartan) After recovery from the acute attack the disease has a *tendency to become chronic with occasional* relapses

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Epidemiology Malaria at the present time is one of humanity s chief scourges and there are many fertile areas that remain uninhabitable because of its influence On the other hand the disease has been eliminated from many areas and currently the World Health Organization has undertaken a world wide program In the United States indigenous malaria has practically disappeared

Malaria in World War II The introduction of American troops in World War II into South Pacific areas Africa Middle East China Burma and India resulted in thousands of malarial infections Malaria soon became the outstanding medical problem of the war not from the standpoint of mortality because there were relatively few deaths but because of the high degree of morbidity The most disturbing feature was *the great number of vivax relapses which* occurred at periodic intervals usually every four to six weeks For several years after World War II and the Korein conflict there was a considerable residue of men with relapsing infections Some of these patients experienced as many as forty or more distinct episodes

The malaria acquired overseas was both the falciparum and the vivax variety As the former has an extremely low relapse *rate practically all malaria seen in the* United States is the less severe and more persistent vivax form A noticeable feature of the malaria seen in the returning service man is the absence of malarial cachexia so prevalent in populations native to endemic areas Enlarged spleens anemia and other commonly associated debilities are not frequently encountered even in servicemen with a long history of malaria This suggests that cachexia develops only when *malaria is associated with other infections* or poor nutritional states

Etiology The specific etiological agent of malaria is a unicellular organism which lives at the expense of the erythrocytes in certain reptiles birds and mammals and belongs to the order of Hemosporidia class Sporozoa and the single genus Plasmodium The species within the genus are not numerous and they are capable of producing infections only in hosts that are closely related In man malaria is produced by four specific parasites known as *Plasmodium vivax P malariae P falciparum* and *P ovale* There are certain similarities among these parasites but each has a distinct morphology and definite *pathogenicity and none of them* has been found infectious for any of the lower animals Unlike viral or bacterial diseases the etiological agent *of malaria has not* been successfully cultivated on an artificial medium or in the presence of living cells outside its respective host *The only means* of transmission in nature is by anopheline mosquitoes although different species act as vectors in different parts of the world The anopheline mosquito does not act as a mere mechanical transmitter of the pathogen from man to man but serves as a haven where the parasite undergoes a definite development necessary for the perpetuation of the organism An artificial method of transmission is the hypodermic

syringe commonly used by drug addicts which results in the actual transfer of infected blood from a carrier to a susceptible person This type which occurs more often in the larger cities is responsible for many deaths since it is usually the highly virulent falciparum malaria Less frequently malaria is acquired in nonendemic areas after transfusions from an infected donor There are many authenticated reports of children becoming infected from parent donors who last had symptoms twenty or more years previously It is interesting to note that in practically all such instances the causative agent has been *P malariae*

The Mosquito Host Many different species of anopheline mosquitoes have been described from various parts of the world Although most of them can transmit malaria they vary enormously in their susceptibility In North America *Anopheles quadrimaculatus* has been shown to be the only important vector The habitat of this mosquito extends to the southern border of Canada but the severe winters in addition to agricultural drainage and clearing have largely limited its activity as a disease carrier to the southern states The adult anopheline mosquito is identified by its spotted wings and its habit of resting at an angle Only the female mosquito can become infected since she requires a blood meal to produce fertile eggs The male is not bloodsucking Anopheline mosquitoes lay their eggs in swamps ponds and streams the larvae lie and feed horizontally on the surface of the water a characteristic which makes them more liable to destruction by floating larvicides particularly oils and Paris green The common pest mosquito *Culex* lays its eggs in eaves tin cans cisterns or any container of water in and about houses The larvae hang head downward with an air siphon sticking above the surface of the water the body of the adult is parallel to the surface of its resting place It is not concerned with the transmission of malaria and is definitely a domestic mosquito while the anopheline prefers a wilder environment

Development of the Malaria Parasite in the Mosquito In order to become infected a female mosquito must first bite a person who has male and female malaria parasites in the circulating blood since the asexual parasites cannot survive in the mosquito's stomach The sexual form known as gametocytes initiate the cycle of development within the stomach of the mosquito where they undergo fertilization This is accomplished by the male parasite pushing out several flagella which break loose and come into contact with the female form Many attempt to penetrate but when one succeeds the foiled ones depart for other quarry (This also can be observed readily under the darkfield microscope) The fertilized forms then push their way out between the stomach cells and form cysts on its outer wall These cysts known as oocysts gradually enlarge so that by the eighth or tenth day they are mature and measure about 75 μ in diameter If examined under the microscope the oocysts will be seen to be distended with spindle shaped sporozoites At this time they rupture into the body cavity of the mosquito and the liberated sporozoites make their way to the salivary glands where they lie and await an opportunity to enter the blood stream of a susceptible person The sporozoites escape from the salivary glands as the infected mosquito bites a person thus initiating the cycle of development in the human host At this step there is a missing link in the life history of the malaria parasite it was last seen as a spindle shaped sporozoite in the salivary gland of the mosquito and next observed about ten days later as a "ring-shaped" parasite in the human erythrocytes No one has recognized an intermediary form or understood the exact manner in which it attacks the erythrocytes

Malaria Parasites in Man The most common variety is *Plasmodium vivax* About ten days after an infection has been acquired through the bite of an infected anopheline the first parasites are observed in the erythrocytes as circles of cytoplasm with a mass of red chromatin This stage is commonly referred to as the "ring form" There follows a progressive growth of the parasite into an ameboid stage characterized by irregular arrangement of the cytoplasm appearance of pigment granules and enlargement of the chromatin The infected erythrocyte becomes somewhat larger and paler than normal and contains numerous reddish granules known as Schuffner's dots which occur only with this species of parasite As the parasite continues to enlarge the amount of pigment increases and the nucleus starts to divide At the end of forty-eight hours the erythrocyte is a mere membrane all hemoglobin has been devoured or replaced by the parasite The nuclear fragments have assumed a "rosette" form and each unit is known as a *merozoite* which is a daughter parasite As the erythrocyte ruptures the cluster of merozoites usually 16 in number are released and each attaches itself to a new cell The cycle is then repeated every forty eight hours but fortunately for man not every merozoite that is released finds its way unhindered to reproduce its full quota of progeny Fully 90 per cent of the merozoites are destroyed by the macrophages located chiefly in the spleen liver and bone marrow For some unknown reason there is a tendency for the vivax merozoite to prefer a reticulocyte to a mature erythrocyte for initiating its development

The asexual reproduction of the parasite continues for several days when new forms appear the sexual ones (gametocytes) They fill the entire erythrocyte Their pigment is scattered and chromatin is diffuse The male parasite may be differentiated from the female by its pale staining cytoplasm with Giemsa or other Romanowsky stains The gametocytes are concerned only with infection in the mosquito have no clinical importance and usually persist in the blood in limited numbers for two or three weeks The characteristics which dif

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classic features according to the species involved

Vivax or Tertian Malaria This is by far the most common the mildest and most likely to recur Because large numbers of persons have received the beneficial effects of vivax malaria in the treatment of neuro syphilis excellent opportunities have been afforded for observing the symptoms of vivax infections in great detail The most thoroughly studied malaria infections were induced by the bite of infected mosquitoes and once established they were allowed to run their full course in order to obtain greatest therapeutic results In a typical infection about six days after the bite of the mosquito the patient has a mild back ache muscle soreness and a low grade fever without chills Febrile paroxysms appear about the fourteenth day Usually these paroxysms occur on alternate days and co incide with the segmentation of the mature parasite They may occur daily (quotidian) however which means that there are two broods of the same parasite one segment ing on even days and the other on odd days of the disease or the two types may occur during the course of the one infec tion as shown in Figure 40 A typical parox ysm for vivax malaria consists of "cold "hot and "sweating" stages

COLD STORAGE The patient has a chilly sensation over the entire body which grad ually increases in intensity the teeth chat ter the skin becomes blue and cold and there is an uncontrollable shaking In spite of heat pads and blankets it is impossible to keep the patient warm The pulse is rapid and weak and occasionally there are nausea and vomiting The cold stage lasts on the average one hour and subsides as the body temperature rises

HOT STAGE In this stage the patient has a flushed face and severe headache and may be partially delirious with a tempera ture often as high as 107° F There is a sensation of intense heat with a hot dry skin This portion of the paroxysm lasts about two hours

SWEATING STAGE The sweating stage has an abrupt onset and the patient breaks out into a profuse perspiration Temperature drops to normal the headache disappears and a feeling of well being comes over the patient Although somewhat drowsy and weak he feels able to resume work

Quartan Malaria This parasite produces an infection (after a prolonged incubation period) which may vary from eighteen to forty days The onset is similar to that of vivax malaria being initiated by a low grade remittent fever lasting three to five days without chills The paroxysms usually occur every seventy two hours the time required for the complete development of the asexual cycle in the blood However the total period from the beginning of the day of one chill to the end of the day of the next paroxysm is four days (Fig 11) which accounts for the unfortunate name quartan malaria A double quartan infec tion produces a chill on two consecutive days with an intervening day of normal temperature Rarely does one encounter daily chills with quartan malaria When compared with vivax malaria the parox ysm lasts longer is slightly more severe and the patient feels less like leaving his bed between chills

Falciparum Malaria Falciparium or es tivoautumnal malaria is a more severe dis ease than the others and as such is respon sible for the origin of the purely descriptive terms of the disease as cerebral algid hemorrhagic pernicious and many others The latter refer to symptoms which depend largely upon the localization of the para sites The incubation period is commonly twelve days the fever is irregular and not characteristic The paroxysms are similar

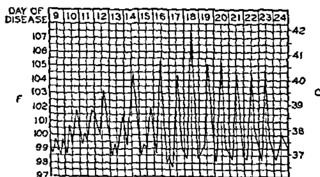


FIG 40 Temperature chart of a patient with vivax malaria showing both tertian and quotidian types of fever (Photograph by J B Haulenbeek)

ferentiate P vivax from other parasites are a forty-eight hour cycle 16 merozoites in the mature parasite at time of segmentation and an enlarged pale parasitized erythrocyte usually stippled with red staining granules

Plasmodium malariae which produces quartan malaria in man requires seventy two hours to complete each asexual cycle in the erythrocyte Except for its slower metabolic activity this parasite bears a close similarity to the behavior of *P vivax* Morphologically *the young parasite is frequently observed as a* band form across the cell The parasitized erythrocyte seems *to have a greater concentration of hemo*globin and is somewhat reduced in size There are usually *only eight merozoites in the mature parasite* and after segmentation they prefer to attach themselves to mature erythrocytes rather than the younger reticulocytes

The asexual cycle of *Plasmodium falciparum* is first recognized as an extremely small "signet ring in the erythrocyte approximately one half the size of a *P vivax* ring Only in the severest cases are the more mature stages of the parasite seen in the erythrocyte The reason for this seems to be that early in the acute infection there is a tendency for the ring forms to aggregate in the capillaries throughout the body where they undergo their usual development The required time for one cycle is not definitely known but is probably between twenty four and forty-eight hours The gametocytes are crescent shaped a definite diagnostic finding since no other known malaria parasite has this morphology The parasite seems to attack young and old erythrocytes indiscriminately

Plasmodium ovale first described in 1923 by Stephens and now generally accepted as a definite species derived its name from the fact that the infected erythrocyte always assumes an oval shape Otherwise its morphology and behavior are practically identical with those of *P vivax*

Morbid Anatomy Patients with tertian or quartan malaria rarely come to autopsy except when the malaria is a contributory cause of death The *pathological lesions in* these instances are in the main due to the disintegration of parasitized erythrocytes and the *accumulation of pigment* The maximum evidence of an active or latent malarial infection is found in the spleen and *because of the collection of* pigment no other disease presents a more pronounced pathognomonic picture either macroscopically or *microscopically* The spleen is usually markedly enlarged slate gray in color and of soft consistency during the acute disease The capsule is smooth and tense and may even rupture spontaneously The cut surface exudes a brownish pulp and the malpighian bodies stand out Microscopically *the sinuses are distended* with parasitized and normal erythrocytes The macrophages are laden with *parasitic debris which is mostly pigment* The liver is usually somewhat enlarged and slightly darker than normal Microscopic *examination reveals that the Kupffer cells* are engorged with parasites in various stages of disintegration There is little or no evidence of toxic degeneration *in the* parenchymal cells The heart lungs kid*neys and pancreas have a normal* cellular structure and the only finding of interest is again the presence of pigment in the active macrophages

Falciparum malaria is responsible for the majority of deaths due to uncomplicated malaria and likewise presents some pathological lesions not present in vivax or quartan malaria Fatal cases are usually associated with an overwhelming infection and cerebral involvement The brain shows a gross brownish discoloration of the gray matter with macroscopic punctuate hemorrhages in the white matter Stained sections reveal the capillaries filled with parasites in various stages of development The cerebral capillary occlusion which is characteristic of falciparum malaria may also frequently be generalized and present a pathological picture of congestion A pathologist is frequently able to make the correct diagnosis of this disease from a glance at the exposed tissues because of the slate gray tinge due to capillary engorgement with pigmented parasites

Symptoms The symptoms of malaria vary according to the type of parasite producing the disease Each of the four parasites has a characteristic behavior and *time of sporulation* which give rise to different clinical pictures Symptoms also vary according to *host resistance or immunity For example* in areas of high malaria endemicity people may go about their work with no apparent *difficulty despite the presence* of a considerable number of circulating parasites in their blood stream Less intense infections gauged by *the number* of circulating parasites will completely prostrate a nonimmune person coming into the same area There is evidence to show that strains of the same species of parasite may also have different virulence However the initial infections in susceptible persons have certain

where the patient resides or that he has traveled in infected areas for example campers and hunters frequently acquire malaria in this manner

There are few physical signs The patient appears anemic the degree varying according to the duration and severity of the disease The spleen if sufficiently enlarged to be palpated is soft in the acute disease and firm in chronic cases

A therapeutic diagnostic test is useful if correctly interpreted If a potent antimalarial drug fails to reduce a patient s fever it is strong evidence that the fever is not caused by malaria Likewise it is extremely important that the physician ascertain whether the patient has taken some remedy on his own initiative before seeking medical aid This self medication is a common practice and accounts for a temporary cessation of symptoms and disappearance of parasites from the blood stream

In addition to the diagnosis of the individual case the physician is frequently called upon to determine the prevalence of malaria in a community The established routine procedure is to determine the incidence of parasitemia (by blood smear examination) in as large a group of persons as is feasible At the same time a determination of the number of enlarged spleens and the degree of splenomegaly furnishes additional information Personal history about malarial infections in previous years is also included Such a survey will give data permitting the quantitative expression of the amount of malaria in a community and if continued will furnish a guide to yearly endemicity of the disease

Prognosis Patients with vivax or quartan malaria rarely if ever succumb unless the malaria is complicated by other diseases malnutrition or exposure Even in endemic areas where many infections are self treated deaths are few Moreover in paretics in whom malaria has been induced for therapeutic purposes and allowed to run a full course without intervention the death rate is almost nil Vivax and quartan malaria are diseases of high morbidity and low mortality

Falciparum malaria is the cause of practically all deaths due to malaria but if recognized early usually responds to therapy A guarded prognosis must be made for patients with the cerebral type in coma or stupor Malaria with hemoglobinuria always presents a grave prognosis

Relapses are to be expected with all types of malaria These may occur at any time but are most likely to occur after exposure change of climate hemorrhage or when body resistance is lowered from any cause

Immunity A malarial infection confers a low grade but specific immunity upon its host after the acute attack has subsided This acquired immunity in man is of short duration and a person may have repeated attacks produced by the same organism within a relatively short space of time In experimental animals the residual immunity following complete eradication of the infection persists only a few weeks Many believe that a host is immune to malaria only in the presence of infection There is no cross immunity in human malaria since it is frequently observed that a person may have a simultaneous infection with two or more types of plasmodia It is highly probable that a person is resistant only to the malaria in his particular locality for example it has been shown that a person immune to a strain of vivax malaria in Florida behaves as a normal when exposed to infection from a vivax parasite from Cuba

The mechanism of immunity in malaria is not clearly understood but it is possible to demonstrate specific protective and complement fixing antibodies and agglutinins in the serum of experimental animals after recovery from the acute attack The chief defense of the body against an acute malarial infection or recovery from a relapse probably depends upon a greatly accelerated rate of phagocytosis by the individual macrophages of the reticuloendothelial system

Treatment The accepted treatment for malaria is the administration of certain chemotherapeutic drugs Specific antiserum prepared from animals or serum from convalescent patients has not proved beneficial in the prevention or treatment of the disease

It is now possible to state that satisfactory suppressive and curative compounds for vivax and falciparum malaria are available There have been insufficient tests of these recently introduced compounds in quartan malaria Moreover preliminary studies indicate that certain of the new compounds are probably true prophylactic agents This would be in contrast to the previously available prophylactic" drugs which did not actually prevent infection but suppressed evidence of disease so long as prophylaxis was continued These goals visualized and sought by malariologists for centuries are now at hand

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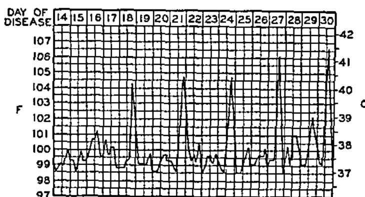


FIG 41 Temperature chart of a patient with quartan malaria

to those accompanying other malarias although of longer duration and occurring at more irregular intervals The temperature is usually high If there is a cerebral localization of the parasites the onset is rapid with delirium or coma and death frequently ensues without a return to consciousness The disease may present a gastrointestinal syndrome with abdominal cramps diarrhea vomiting and only a few parasites in the peripheral blood The patient is markedly dehydrated and may have a high or low grade fever Stools may contain blood resulting from intestinal capillary thrombosis and ulceration

Blackwater Fever Blackwater fever sometimes called hemoglobinuria is the most serious and frequent complication of malaria but occurs almost entirely in the falciparum variety The etiology of blackwater fever is not understood At one time this complication was very prevalent in the United States but it is no longer present there It now occurs only in certain of the more heavily endemic areas of Africa and the Orient Blackwater fever does not appear until the patient has had repeated attacks of malaria The first sign is a pronounced darkening of the urine produced by the hemoglobin released during extensive intravascular hemolysis The blood pigments very rapidly increase in amount in the urine until there is a copious amorphous deposit The pulse becomes very rapid the fever is high 105° F or more and curiously enough parasites are usually absent at this stage The erythrocyte count drops to 2 000 000 cells per cu mm or lower within twenty four or forty-eight hours and vomiting and jaundice are likewise early symptoms The appearance of blackwater fever is associated with a very poor prognosis the mortality being approximately 50 per cent The only known treatment is absolute rest The body fluid should be restored as rapidly as possible preserving normal concentrations of protein and salt Excessive blood transfusions should be avoided since cardiac failure often results

Diagnosis An absolute diagnosis of malaria depends upon the recognition of the parasite in stained thin or thick blood smears Ordinary thin smears should be made on slides that have been thoroughly cleaned to ensure even spacing of the erythrocytes They can be stained with Giemsa s Wright s or Hastings stain For the uninitiated the thin smear method is preferred because there is less opportunity to be confused by artifacts It is easy to overlook parasites by this method however although they may be present in sufficient numbers to produce clinical activity The thick smear method is advantageous because it affords a means of concentrating the blood The thick film should be about the size of a dime on a very clean slide The two preferred methods of staining are Giemsa s and Field s The former is satisfactory and is accomplished by adding one drop of Giemsa to 1 ml of distilled water and staining for thirty minutes Field s method has many advantages long drying of the film is unnecessary the entire staining takes less than 10 seconds and there are fewer artifacts (Consult J W Field *Tr Roy Soc Trop Med* 35 35 1941) The greatest number of parasites appears in the blood stream immediately after the chill and for the following six hours The inability to find parasites in blood films does not exclude the presence of malaria particularly in a subsiding or chronic infection Splenic puncture for diagnostic purposes is unwarranted and dangerous since it may lead to the rupture of an enlarged tense spleen

The chief complaints of the patient are usually severe chill high fever and sweating In the history there also is usually information showing that malaria is endemic

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It is possible to make these statements because of the results of a research program initiated at the beginning of World

War II and continued until the present Nevertheless it would be incorrect to assume that no problems continue to exist for evaluation must continue for years no disease as formidable as malaria is easily conquered

Suppression For the suppression of malaria two compounds *chloroquine* (Aralen) and *amodiaquine* (Camoquin) have had wide laboratory experimental and field trials and thus far have proved to be eminently satisfactory The use of chloroquine was compulsory among the troops in the endemic areas of Korea Malaria although acquired remained at subclinical levels and no problem was recognized until infections appeared in this country among those exposed and who had discontinued the drug The suppression of malaria is indicated in persons traveling or living in endemic areas of malaria such as soldiers laborers and others Thus far neither chloroquine nor amodiaquine has been used on a large scale in native populations Both of these drugs require only one dose weekly are readily absorbed and have not been observed to produce any untoward or disagreeable side effects

The dosage of chloroquine diphosphate (Aralen) is 0 5 gm (two tablets) weekly taken the same day each week For heavily endemic areas the dose can be increased by one to two tablets for adults Amodiaquine (Camoquin) 4 [7 chloro 4 quinolylamino] a diethylamino o-cresol is also equally effective at two or three tablets (0 4 to 0 6 gm) once weekly

Pyrimethamine (Daraprim) a new compound has had considerable trial and is very useful as a suppressive agent but it is contraindicated for the therapy of the acute illness because of its slow action Moreover in experimental infections strains of parasites resistant to this drug have emerged

Therapy for the Acute Attack Either chloroquine or amodiaquine is recommended for an acute attack of malaria either for the first illness or a relapse The therapeutic action of these drugs is exceedingly prompt without toxic reactions Neither of these compounds will result in an eradication of infection for vivax malaria but will do so for falciparum infections

The usual chloroquine regimen consists of an initial dose of 1 0 gm (four tablets) followed by 0 5 gm (two tablets) after six hours On the second and third day 0 5 gm (two tablets) is given

Quinine and quinacrine (Atabrine) are inferior to the more recently discovered compounds and are not recommended

Radical Cure Vivax malaria has a constant tendency to relapse despite treatment with the maximal tolerated amounts of antimalarial drugs and their administration over an extended period The only drugs thus far shown to be effective in the complete eradication of a chronic vivax malaria are the 8 aminoquinoline compounds Pamoquine (Plasmochin) was the first to be recommended but has now been discarded in favor of *primaquine* a more effective and less toxic derivative Primaquine has been tested in many thousand white and nonwhite persons and found to be a safe compound when given in the recommended dosage When tested for its curative value in experimental and naturally acquired infections it was demonstrated to be effective In doses of 15 mg (base) daily for fourteen days primaquine has reduced the relapse rates in Korean vivax malaria to less than 1 per cent by destroying the tissue stages of the parasite Since primaquine is relatively ineffective against the asexual blood stages it should be used in combination with chloroquine The recommended multiple drug therapy consists of the same chloroquine or camoquine regimen as used in acute attacks and the additional concurrent administration of primaquine (15 mg) each day for a total period of fourteen days

The general treatment consists of simple measures aimed at keeping the patient comfortable especially during the acute paroxysms In infections complicated by vomiting or diarrhea special effort should be made to combat dehydration It is advisable that convalescent patients receive iron in any of the available forms since it is extremely beneficial in the restoration of hemoglobin deficiency

L T COGGESHALL

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Trypanosomiasis

African trypanosomiasis Chagas disease and *Trypanosoma rangeli* infections will be discussed in this section The last named now considered nonpathogenic is cited only as it concerns differential diagnosis

AFRICAN TRYPANOSOMIASIS

(African Sleeping Sickness Maladie du Sommeil Schlafkrankheit)

Etiology Two species of Trypanosoma are currently recognized as the etiological agents of African trypanosomiasis *T gambiense* of irregular distribution throughout tropical Africa and *T rhodesiense* reported only from East Africa Both species occur in man as polymorphic but typical trypanosomes 15 to 33 μ in length Multiplication takes place in the blood by longitudinal division into two or occasionally three or more trypanosomes

So far as is known there are no obligatory intracellular tissue stages of these two trypanosomal infections such as are observed with *T cruzi* Both African species may be maintained either in cultures or frozen at $-70°$ C for indefinite periods

Another cycle of development takes place in Glossina (tsetse) biting flies at present established only in Africa Trypanosomes taken in with the blood subsequently undergo extensive migrations in the fly meanwhile changing morphologically multiplying losing and then regaining infectivity Eventually the trypanosomes invade the salivary glands of the fly and are inoculated at the next feeding This cycle in Glossina requires ten to thirty five days or more Both sexes are hematophagous and serve as vectors The infection is not hereditary in the fly

Epidemiology African trypanosomiasis is contracted following the bite of an infected Glossina occasionally congenitally and rarely through blood transfusions or other accidental inoculations

The distribution of the disease depends upon requirements and preferences of the fly *G palpalis* a riverine species may not penetrate adjacent forested areas for more than 200 yards *G tachinoides* likewise riverine requires less moisture and is more hardy than *palpalis* These are the two most important vectors of *T gambiense* The principal vectors for *T rhodesiense* (*G morsitans pallidipes* and *swynnertoni*) are savanna species and can thrive even when the environment is very dry part of the year The flies are now believed to have preferences for certain types of vegetation a matter of importance in control For these reasons the disease incidence tends to be spotty it is endemic in one spot and another area close by may be free Occupation is important in so far as contact with Glossina is favored The disease occurs essentially in lightly settled areas and urbanization automatically establishes conditions unfavorable for Glossina once a minimum population density is exceeded

Animals furnish blood for Glossina although they are currently considered not to be significant reservoirs of *T gambiense* but more important for *T rhodesiense* Much of these data require re-evaluation because of recent knowledge of food preferences

Pathology In African trypanosomiasis lymph node lesions are customary if not distinctive the reticuloendothelial elements are increased and numerous macrophages occur in the sinuses some containing erythrocytes and leukocytes Later sclerosis producing bands of connective tissue gives the nodes an alveolar appearance

Brain lesions are most marked in prolonged cases The meninges may be thick and adherent opaque or simply edematous the maximal changes occur over the convexity The brain at times edematous less frequently shows small hemorrhages and areas of softening The characteristic microscopic finding is a perivascular infiltrate which occurs at all levels (also in the medulla) in which plasma cells are conspicuous and may predominate Mott s morular cells (Russell bodies) are found in the infiltrate scattered throughout the brain and in the cerebrospinal fluid

A pancarditis with myocardial predominance has been described particularly in *T rhodesiense* cases The lesion combines a predominantly mononuclear cell infiltration with a progressive sclerosis

The cerebrospinal fluid shows a progressive increase in cells initially then in protein globulin tests are positive as are various colloidal reactions Dextrose and chloride values are usually low The plasma globulin increases the albumin is normal or reduced the erythrocyte sedimentation rate increases Cold hemagglutinins are frequently present

Signs and Symptoms The initial lesion at the site of an infected Glossina bite develops and completely regresses in about two weeks At peak development the area is raised reddened and circular may reach a diameter of 8 cm or more and has a darker center The lesion contains numer

ous trypanosomes by the fourth or fifth day —that is before they are usually seen in the blood

If the initial lesion is not perceived as often happens the disease appears to start with constitutional symptoms these are extremely variable as to intensity and time of onset Fever pain disturbances of the sleep pattern asthenia skin rashes anemia edema particularly about the eyes and enlargement of the lymph nodes all occur frequently The most constant and distinctive sign during the early stage is enlargement of the lymph nodes The node draining the initial lesion is first affected later there is generalization The appearance of enlarged posterior cervical nodes during the stage of generalization is known as Winterbottom s sign

Usually the nodes are only moderately enlarged (15 to 20 mm long) They are freely movable firm and elastic and somewhat painful spontaneously while enlarging but later are painful only on pressure The nodes do not suppurate unless secondarily infected but eventually become fibrous and harder

Meanwhile clinical manifestations reflect the attack on the central nervous system Tremors deep hyperesthesia with delayed onset (Kerandel s sign) and persistent headache may be accompanied by abnormal cerebrospinal fluid findings even early in the course of the disease Romberg s sign patellar and ankle clonus and various types of paralyses or pareses occur later Functional difficulties in walking and in speech result the mentality is affected reflection becomes difficult and there may be abrupt changes of character as well as psychic disturbances

Spontaneous regression is reported but the disease is usually considered to evolve fatally if untreated Nevertheless the progress of the disease is extremely uneven In certain *T gambiense* areas some infected persons may not plead illness and may perform hard manual labor for years whereas others are severely affected With *T rhodesiense* the untreated patient may die in six weeks

Diagnosis Diagnostic techniques in current use depend upon the visual recognition of trypanosomes in blood cerebrospinal fluid lymph node aspirate and more rarely in bone marrow Blood is examined fresh then if necessary as a hemolyzed stained thick drop If these examinations fail citrated or heparinized blood can be centrifuged three times first at 1000 rpm for three minutes this is repeated on the supernate finally the trypanosomes are sedimented by twenty minutes at 1500 rpm The cerebrospinal fluid examination usually requires centrifugation

Lymph node puncture is best performed on a node which is large and soft using a medium caliber needle (e g a U S No 19) about 2 5 inches long After skin disinfection the node is held firmly from below by the fingers of the left hand The sterile needle (without attachment to a syringe) is then inserted rotated and given a few to and fro movements With proper illumination it is possible to see into the shaft and determine whether the puncture has been productive After withdrawal a syringe is fitted the contents expelled and examined If the procedures described are inconclusive mice or rats guinea pigs rabbits or monkeys may be inoculated

Evaluation of these classic methods of diagnosis has become possible with the advent of cultural methods Conventional methods may fail to detect 15 to 20 per cent of the cases may fail to detect trypanosomes in 30 per cent of infected cerebrospinal fluids and not infrequently may result in negative reports on inoculated animals that have developed a latent type of infection The cultural method is not in general use consequently when clinical suspicions are aroused but not confirmed by the laboratory repetition of the conventional procedures should be insisted upon

Prognosis The earlier trypanosomiasis is treated the more favorable the outcome Protein estimations of the cerebrospinal fluid furnish a rough guide to the degree of central nervous system damage when the cerebrospinal fluid contains 30 mg of protein it is essential to choose a chemotherapeutic agent which will cross the blood brain barrier

Treatment Because of the toxic potential of certain of the drugs used only proved cases of trypanosomiasis should be treated It is important to follow the cell count and protein content of the cerebrospinal fluid with (1) a pretreatment examination (2) a second examination at the end of therapy and (3) a third examination one year or preferably fifteen months later It may not be possible to restore the cerebrospinal fluid to completely normal values but a cell count above 10 with a protein value of 25 mg does not signify cure Agents of possible value in combating drug toxicity should be at hand and if the patient is not hospitalized he should be interviewed daily for evidence of drug intolerance

The introduction by Friedheim of the

Melarsen compounds is resulting in a change in chemotherapeutic practice although the optimal doses of these drugs are not yet agreed upon The compounds (Melarsen and Mel B) and tryparsamide penetrate into the central nervous system in effective amounts whereas suramin sodium (Antrypol Bayer 205) and pentamidine do not

Suramin sodium followed by tryparsamide is widely used however effective doses vary in different areas In one satisfactory schedule suramin sodium is dissolved in sterile distilled water just before use 1 0 gm in 10 ml and all is injected intravenously Three such doses are given the second dose three weeks after the first if this is practicable or if not after five days and the third dose five days later Tryparsamide is then administered freshly dissolved in distilled water to make a 20 per cent solution Two grams the usual adult dose is injected intravenously or if need be intramuscularly and repeated every five to seven days to a total of 20 to 45 gm The precise total varies according to the previous therapeutic results in the area the response observed and the previous treatment received Poor results can be anticipated in *T rhodesiense* infections and from tryparsamide resistant strains in which cases Melarsen compounds are used *The most common toxic complication of tryparsamide therapy is optic atrophy* patients should be questioned before each dose to detect suggestive symptoms Immediate stoppage of treatment may not arrest the optic neuritis and dimercaprol should be employed

Mel B a tervalent arsenical composed of melarsen oxide coupled with dimercaprol is effective at all stages of the disease acts against both *T gambiense* and *T rhodesiense* and also against tryparsamide resistant strains of trypanosomes It is provided as a 3 6 per cent solution in propylene glycol and injected intravenously In advanced *T rhodesiense* cases the following schedule has given satisfaction 2 5 ml of the 3 6 per cent solution of Mel B daily for three days then one week rest followed by 3 0 ml 4 0 ml and 5 0 ml on successive days another week of rest and three daily injections of 5 ml each to total 34 5 ml or 1242 mg for a 50 kg patient If urgent treatment is not required pretreatment with suramin sodium (Antrypol) is advantageous Mel B has also been satisfactory in the treatment of advanced *T gambiense* cases

Melarsen a quinquevalent arsenical has been recommended for field use in doses not exceeding 20 mg per kg of body weight in a series of twelve injections each given at five-day intervals It has proved valuable in areas where relapses from the tryparsamide treatment of *T gambiense* infections were a serious problem

Prophylaxis and Control Chemoprophylaxis in African sleeping sickness is one of the great achievements of chemotherapy Three compounds have been produced which following a single injection will protect against trypanosomal infection for at least two months and perhaps more two of these have been widely used in man Pentamidine perhaps the most used today is administered as an aqueous solution usually of the isethionate intramuscularly and sometimes intravenously in a dosage of 3 0 mg per kg of body weight Suramin sodium (Antrypol) is given in a one gram dose as previously described Neither prophylactic should be administered except after full assurance that the patient is not already infected otherwise this treatment may mask the infection which will progress and become more of a therapeutic problem

Area control of the disease has been based on chemoprophylaxis combined with chemotherapy This is an excellent rapid manner of controlling an outbreak If the chemoprophylaxis is continued infection rates in the exposed population may fall to extremely low levels and remain low so long as the chemoprophylaxis is adequately maintained Antiglossina measures involve the use of insecticides such as dieldrin (used at times in "preferential spraying" only) clearing of the vegetation and wholesale killing of game One interesting procedure involves resettlement into relatively dense population centers it being considered that once such centers are rendered fly free normal human activities will be so unfavorable to the fly that its re-entry will be permanently prevented

CHAGAS DISEASE

Chagas disease caused by *Trypanosoma (Schizotrypanum) cruzi* is a progressive noncontagious insect transmitted disease established in rural areas of the Americas In the United States although *T cruzi* is enzootic in the Southwest reports of human disease are rare On presumptive evidence the infection is believed to occur in Asia

Etiology *Trypanosoma cruzi* is a typical trypanosome with the following distinctive characteristics (1) the undulating membrane is scanty with few or no folds (2) the kinetoplast is extremely large *i e* ap

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In the brain T cruzi situated intracellularly is not invariably directly associated with the widespread inflammatory foci which occur at all levels T cruzi has also been reported from smooth and striped muscle ovaries adrenal cortex bladder thymus liver spleen lymph nodes blood vessels skin lacrymal glands and conjunctivae

Diagnosis The diagnosis of Chagas disease usually is made by examination of the blood more rarely by examination of the cerebrospinal fluid or biopsy material The blood specimen is preferably taken during fever if negative by direct examination it should be prepared as one or more thick drops if necessary this may be repeated on specimens from the buffy coat after light centrifugation of citrated blood

Cultures frequently succeed when direct examination fails 1 0 to 2 0 ml of citrated or heparinized blood are inoculated directly onto each of a half-dozen blood agar slants (N N or N N N) incubated at 22 to 25 C in the dark and examined weekly for eight weeks Animal inoculation is also serviceable Mice and guinea pigs are the most used and young animals are preferred young dogs are reported to be the most susceptible Xenodiagnosis introduced by Brumpt is one of the most sensitive of all methods but requires a specialized laboratory for it requires the feeding of laboratory reared uninfected vectors on the suspects

If trypanosomes are detected by any of the foregoing methods care is required to distinguish *T cruzi* from *T rangeli* which occurs in several of the endemic areas of Chagas disease *T rangeli* about 30 μ in length is about one third longer than *T cruzi* contains a small subterminal kinetoplast and shows dividing forms in the blood

Because the preceding methods may fail the complement fixation method (Guerreiro-Machado reaction) is widely utilized in one form or another It is reported to give false positive reactions in leishmaniasis and also in chancroid furthermore the significance of a positive reaction in *T rangeli* infections remains to be evaluated False negative reactions are said to be rare during the acute phase but a negative reaction during the chronic period is difficult to evaluate

Treatment There is no satisfactory treatment for Chagas disease the unsolved problem being the eradication of *T cruzi* in intracellular foci The following are said to have activity on the forms in the peripheral blood primaquine pentaquine 7602 and 9736 (Bayer) and Spirotrypan (Hoechst)

Prevention Prophylactic and control measures are centered on vector control Dwellings should be made as insect proof as possible and then benzene hexachloride (gammexane) or dieldrin both of which have residual effects can be applied with satisfactory effect Infected domestic animals should be destroyed and dwellings adequately protected from re-entry of the insects particularly from animal shelters Individual prophylaxis in an endemic area involves the avoidance of infected habitations fine mesh bed nets are effective and it is probably wise to carry a portable bed or hammock and be prepared to sleep al fresco

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Leishmaniasis

The diseases described under this title are all caused by infection with parasites of the protozoon genus Leishmania A number of specific names have been given to parasites recovered from patients with differing clinical conditions in various parts of the world and in addition from dogs Such species however have not so far been satisfactorily distinguished At present three species are generally recognized corresponding to the three diseases described below namely kala azar oriental sore or cutaneous leishmaniasis as seen in Mediterranean and Asiatic areas and American or mucocutaneous leishmaniasis as seen in South and Central America It should be noted that in certain circumstances cutaneous and mucocutaneous lesions occur in kala azar and that visceral involvement has been reported in American mucocutaneous leishmaniasis The separation of these diseases and of the parasites associated with them rests on epidemiological clinical and immunological grounds

proximately the size of the nucleus and (3) dividing forms do not occur in the blood

Multiplication of the trypanosome in man is cyclical and takes place intracellularly in the tissues particularly in the heart Apparently the trypanosome penetrates within the myocardial fiber there leishmania leptomonas and crithidia forms develop and finally the mature trypanosomes which are discharged into the blood

The insect cycle commences when the blood trypanosomes are taken up by Triatoma or related *Reduviidae This cycle also is multiplicative* and after a complicated series of changes in the trypanosomes and of migrations in the intestine infective forms are finally produced which are discharged in the feces of the insect The trypanosomes are not inoculated accordingly the rapidity with which the insect defecates after feeding determines in part its importance as a vector

Epidemiology *Trypanosoma cruzi* occurs naturally in man other animals and hemipterous insects of the family Reduviidae The latter consisting chiefly of Triatoma Panstrongylus Rhodnius and related genera are winged capable of short flights and hematophagous at all stages Some are forest dwellers most of epidemiological importance are associated with man in rural dwellings but some have adapted themselves to life in cities Their habits are much like those of bedbugs they feed at night or in the dark and seek shelter by day

The insects also feed on a variety of animals wild and domestic some of which develop chronic infections with *T cruzi* and thus serve as reservoirs At least thirty eight species of animals are naturally infected and a number of others are known to be susceptible Of domestic animals dogs and cats are important reservoirs of wild animals armadillos are often found to carry *T cruzi* in the United States armadillos house mice a species of opossum and several species of wood rat have been found to be infected

Clinical Description The initial lesion of Chagas disease involves the eye in 25 to 75 per cent of cases according to the areas from which the reports are obtained Characteristically the ocular involvement is unilateral accompanied by marked periorbital *edema with reddening of the skin satellite* adenopathy and often with enlargement of the lacrymal gland Pain is usually lacking or mild although there may be slight conjunctival discharge marked inflammation suggests another etiology These symptoms referred to as the *Chagas Romana sign* persist from one to three months and are accompanied by *fever*

In about 20 per cent of the cases the initial lesion is cutaneous often occurring on exposed areas of skin Starting as a small red violet macule somewhat painful and hot it enlarges without becoming appreciably elevated retaining its dark central portion and in a week reaches a diameter of 4 to 7 cm *the skin* and surrounding tissue being indurated for a few centimeters beyond Regional adenopathy is frequent After two weeks or so the lesion crusts over desquamates and regresses slowly often leaving a pigmented scar An *onset with* polyserositis and edema is more unusual in nurslings there are often no external manifestations

Acute stage symptoms frequently merge with those of the initial lesion In the acute common type of the disease after an onset as described there are intermittent fever often recurring as short bouts throughout a long period edema generalized enlargement of the lymph nodes short lived exanthemata of various types nodular subcutaneous elements (chagomas) and occasionally ulcerative lesions *The meningoencephalitic acute type* which occurs most often in nurslings and the very young has convulsive seizures as the oustandin symptom and is often fatal patients who recover frequently suffer from permanent mental or physical defects

Cardiopathy is the conspicuous finding in Chagas disease It occurs in both the acute and chronic forms and is the most important source of symptoms in the chronic *phase The age group involved is from* ten to forty five years The symptoms which vary with the localization and intensity of the lesions consist of palpitation dyspnea epigastric and precordial pain more rarely vertigo and syncope and later the evidences of peripheral congestive cardiac failure Roentgenographic examination often shows some degree of *cardiac enlargement* with predominance in the transverse diameter and for the right ventricle Electrocardiographic changes are extremely frequent and at times are the only way of detecting the lesion Arrhythmias of various types are outstanding and particularly common are disturbances following heart *block* The evolution *of these cases* is extremely variable In Brazil and Argentina the prognosis as regards both invalidism and early death is reported to be distinctly poor elsewhere very nearly total recovery is considered common if not the rule

Pathology In the heart where lesions are the most frequent and noteworthy the *findings are* of three chief types (1) an inflammation predominantly interstitial at the outset (2) destruction of muscle fibers and (3) the etiological agent *T cruzi* which may not be found in any other site The cellular infiltrate is predominantly mononuclear it involves all three cardiac layers but has a myocardial predominance The inflammation both diffuse and focal may be extremely intense Muscle fibers first lose their cross striation and stain strongly with eosin subsequently they rupture retract and form rounded masses or balls *the necrotic* material sometimes occurring within phagocytes *T cruzi* occurs within muscle fibers in collections varying in size up to about 85 by 11 μ these collec

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Epidemiology *Trypanosoma cruzi* occurs naturally in man other animals and hemipterous insects of the family Reduviidae The latter consisting chiefly of Triatoma Panstrongylus Rhodnius and related *genera are winged capable of short flights* and hematophagous at all stages Some are forest dwellers most of epidemiological importance are associated with man in rural dwellings but some have adapted themselves to life in cities Their habits are much like those of bedbugs they feed at night or in the dark and seek shelter by day

The insects also feed on a variety of animals wild and domestic some of which develop chronic infections with *T cruzi* and thus serve as reservoirs At least thirty eight species of animals are naturally infected and a number of others are known to be susceptible Of domestic animals dogs and cats are important reservoirs of wild animals armadillos are often found to carry *T cruzi* in the United States armadillos house mice a species of opossum and several species of wood rat have been found to be infected

Clinical Description The initial lesion of Chagas disease involves the eye in 25 to 75 per cent of cases according to the areas from which the reports are obtained Characteristically the ocular involvement is unilateral accompanied by marked periorbital edema with reddening of the skin satellite adenopathy and often with enlargement of the lacrymal gland Pain is usually lacking or mild although there may be slight conjunctival discharge marked inflammation suggests another etiology These symptoms referred to as the *Chagas Romana sign* persist from one to three months and are accompanied by fever

In about 20 per cent of the cases the initial lesion is cutaneous often occurring on exposed areas of skin Starting as a small red violet macule somewhat painful and hot it enlarges without becoming appreciably elevated retaining its dark central portion and in a week reaches a diameter of 4 to 7 cm the skin and surrounding tissue being indurated for a few centimeters beyond Regional adenopathy is frequent After two weeks or so the lesion crusts over desquamates and regresses slowly often leaving a pigmented scar An onset with polyserositis and edema is more unusual in nurslings there are often no external manifestations

Acute stage symptoms frequently merge with those of the initial lesion In the acute common type of the disease after an onset as described there are intermittent fever often recurring as short bouts throughout a long period edema generalized enlargement of the lymph nodes short lived exanthemata of various types nodular subcutaneous elements (chagomas) and occasionally ulcerative lesions *The meningoencephalitic acute type* which occurs most often in nurslings and the very young has convulsive seizures as the oustanding symptom and is often fatal patients who recover frequently suffer from permanent mental or physical defects

Cardiopathy is the conspicuous finding in Chagas disease It occurs in both the acute and chronic forms and is the most important source of symptoms in the chronic phase The age group involved is from ten to forty five years The symptoms which vary with the localization and intensity of the lesions consist of palpitation dyspnea epigastric and precordial pain more rarely vertigo and syncope and later the evidences of peripheral congestive cardiac failure Roentgenographic examination often shows some degree of cardiac enlargement with predominance in the transverse diameter and for the right ventricle Electrocardiographic changes are extremely frequent and at times are the only way of detecting the lesion Arrhythmias of various types are outstanding and particularly common are disturbances following heart block The evolution of these cases is extremely variable In Brazil and Argentina the prognosis as regards both invalidism and early death is reported to be distinctly poor elsewhere very nearly total recovery is considered common if not the rule

Pathology In the heart where lesions are the most frequent and noteworthy the findings are of three chief types (1) an inflammation predominantly interstitial at the outset (2) destruction of muscle fibers and (3) the etiological agent *T cruzi* which may not be found in any other site The cellular infiltrate is predominantly mononuclear it involves all three cardiac layers but has a myocardial predominance The inflammation both diffuse and focal may be extremely intense Muscle fibers first lose their cross striation and stain strongly with eosin subsequently they rupture retract and form rounded masses or balls the necrotic material sometimes occurring within phagocytes *T cruzi* occurs within muscle fibers in collections varying in size up to about 85 by 11 μ these collec

and thymol turbidity tests are strongly positive The latter must be interpreted in the light of the marked hyperglobulinemia The urine shows nothing remarkable

Patients with kala azar have a decided lack of resistance to other infections It is usually considered that those who have recovered are immune to further infection with kala azar but not to other forms of leishmaniasis

Symptoms In the proper sense of the term the incubation period is not definitely known Symptoms have appeared from three weeks to nearly three years after exposure but the long silent periods should be attributed in part to latent disease The onset is often sudden with fever and chills but it may be insidious The diagnosis is occasionally made by accident in asymptomatic patients Symptoms may be apparently precipitated by unusual exertion or stress The temperature chart usually shows remittent or intermittent fever There may be wide daily swings but sustained elevation occurs in some cases Double or triple temperature peaks in twenty four hours are not infrequently seen Chills sweats dizziness and headache are common Other symptoms include malaise vague pains in muscles bones or joints conjunctivitis coryza cough bleeding from the nose or gums abdominal distention or the presence of an abdominal mass occasionally nausea and vomiting Mental changes are rare except that young children may show clouding or rarely convulsions In many cases symptoms are strikingly vague or few On examination patients often appear remarkably well in spite of fever Pallor accompanies anemia Purpura is occasionally present Petechiae are unusual findings Rose spots do not occur Jaundice is rare In late cases the skin may become dark the hair may fall and there is often much loss of weight Some patients show painless enlargement of groups of lymph nodes Subcutaneous nodules are found in a few cases The pulse rate is increased with fever Rales may be heard in the lungs In the great majority of cases the outstanding physical signs are splenomegaly and hepatomegaly Both organs may enlarge rapidly but the diagnosis has been made when enlargement was not detectable These organs are not usually tender but occasionally a new infarct produces splenic tenderness Ascites and edema are rare

In the Sudan some patients with general manifestations of kala azar have cutaneous and mucocutaneous lesions containing L D bodies In this area and in central Asia a primary cutaneous lesion has been described in some cases

Course and Complications In the absence of treatment the course is usually prolonged often as much as two or three years Remissions and relapses are common Fulminating cases are occasionally seen The commonest complications are bronchitis and pneumonia The rare development of agranulocytosis has already been noted Stomatitis and noma may appear in children with advanced disease Nephritis is an occasional complication An interesting sequel to kala azar postkala azar dermal leishmaniasis has been seen especially in India This condition develops a year or more after recovery from the generalized disease The lesions which take various forms and are considered to be distinct from those of oriental sore contain Leishmania but are not accompanied by any evidence of visceral infection The commonest types are hypopigmented macules a butterfly erythema on the face and relatively later nodules which resemble those of leprosy The nodules may persist for years

Diagnosis A sojourn or residence in an endemic area fever splenomegaly granulocytopenia and hyperglobulinemia should suggest the possibility of kala azar Double daily temperature peaks should bring the disease to mind but they are not pathog

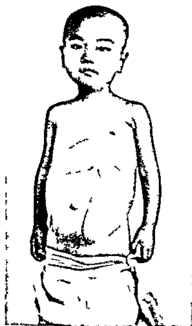


Fig 42 Kala azar in a Chinese child Note protuberant abdomen with enlargement of liver and spleen (Photograph by E B Struthers)

KALA AZAR

(*Visceral Leishmaniasis*)

Definition Kala azar is a chronic infection caused by *Leishmania donovani* with *its principal seat in the reticuloendothelial* system It may affect all the parts of the body and should be regarded as a general disease The outstanding characteristics are fever enlargement of spleen and liver leukopenia anemia and hyperglobulinemia

Etiological Agent The discovery of the causative agent was reported in 1903 by Leishman and Donovan independently *Leishmania donovani* is a parasitic protozoon which is found in two forms during its life cycle In man and other susceptible vertebrates the parasites have roughly oval shapes are about 3 μ long and have no flagella (Leishman Donovan bodies) With Wright or Giemsa stains Leishman Donovan (L D) bodies have pale blue cytoplasm and bright red nuclei the presence of a kinetoplast which appears as a purplish dot is important In appropriate insects and in cultures the organisms have spindle like shapes are 14 to 20 μ long and have prominent flagella (leptomonad forms) Neither form has been found outside animal hosts Both forms succumb rapidly in water or soil A number of animals are susceptible to artificial infection with either of these forms certain hamsters being the most useful Cultures are readily made starting with either form of the parasite

Epidemiology Kala azar is widespread but the areas in which its existence is well known are discontinuous and the importance of the disease varies greatly in localities relatively near one another *The incidence is especially high in parts of China north of the Yangtse River and of eastern India* particularly in Bihar Bengal and Assam The disease is endemic in the region about Tashkent in southern Asiatic Russia and occurs in Mesopotamia Arabia and Turkey It is present in areas scattered all around the Mediterranean Sea and in a belt across Africa from Eritrea and Kenya through Abyssinia and French Equatorial Africa to Nigeria Cases have been reported from Argentina Paraguay Bolivia Brazil Venezuela and Colombia but so far the disease does not seem to be very important in South America Autochthonous cases have not been found in the United States but many imported cases have been reported especially in soldiers previously stationed in endemic areas Kala azar is predominantly a disease of childhood and youth but cases occur at all ages There is no evidence of any variation in *susceptibility* between the sexes or among races Multiple cases have a tendency to occur in small foci and even in particular houses Occasionally the disease appears in epidemic form

Sandflies of the genus *Phlebotomus* have been shown to be important vectors of kala azar in India and China Since various species of Phlebotomus exist wherever the disease occurs these insects may be vectors in other areas In China and elsewhere a natural reservoir host for *Leishmania* has been found in dogs in addition to that in infected human beings Visceral leishmaniasis has been found in a dog imported into the United States from Greece In endemic areas in India however dogs apparently rarely harbor the infection It is generally assumed that in India kala azar *is transmitted* by sandflies directly from patient to patient This may be one of the methods of infection in all endemic areas Although parasites are present in the stools urine and nasopharyngeal secretions of patients there is no evidence that infection arises from these sources The disease has been inadvertently transmitted by blood transfusion

Morbid Anatomy The principal reaction of the tissues is marked proliferation of the cells of the reticuloendothelial system Leishman Donovan bodies may be found in all parts of the body but they are overwhelmingly localized in the cells of this system Intracellular parasites grow and multiply while the host cells gradually swell and finally disintegrate The reticuloendothelial proliferation is often so great that other cells are encroached upon or crowded out The process is most severe in the spleen liver and bone marrow In the spleen and liver marked congestion develops with enlargement which may be enormous Capsular thickening causes these organs to become firm

Pathological Physiology and Chemistry The most important abnormalities are found in the blood About 90 per cent of patients have leukopenia which is largely due to reduction in the number of granulocytes Leukopenia usually develops early After the disease is established counts of 3000 or less per cu mm are common In rare instances agranulocytosis is seen A normal leukocyte count or a moderate elevation is sometimes associated with the presence of an intercurrent infection There is usually a relative lymphocytosis sometimes an absolute increase is seen The same changes occur in the mononuclears Occasionally (but usually with difficulty) parasitized macrophages or mononuclears are seen in blood smears Anemia is also characteristic It develops more slowly than leukopenia and may be absent or trivial in early cases As a rule after the first month hemoglobin values are 40 to 60 per cent of normal and erythrocyte counts are from 2 to 4 million per cu mm The icterus index is normal Thrombocytopenia is regularly present bleeding times and clotting times are in the upper range of normal or somewhat elevated and clot retraction may be defective but these changes are seldom extreme Serum proteins show an increase in globulin (chiefly in the gamma component) which may be so marked that total globulin amounts to 8 or 9 gm per 100 ml Serum albumin is usually decreased especially in longstanding cases A cold precipitable protein has been found in some serums Bromsulfalein tests give normal results while cephalin flocculation

about 98 per cent of patients (including patients with relapses who are retreated) with the exception that this high cure rate has not been attained in the Sudan where fulminating and drug resistant cases are apparently numerous

Treatment When fever severe anemia or leukopenia or serious complications are present patients should be kept in bed Special care should be given to the mouth Blood transfusions are indicated for severe anemia leukopenia or bleeding tendency An antimicrobial drug may be given for an intercurrent infection at the same time as treatment for kala azar Patients with noma should receive penicillin Chemotherapy should be started as soon as the diagnosis of kala azar is established unless agranulocytosis is present Therapeutic tests and "tinkering treatment are especially unwise If it is considered necessary to begin treatment without demonstration of the parasite a full course of the drug in adequate dosage should be given

Effective therapy of kala azar began with the use of antimony and potassium tartrate but this drug was superseded long ago by pentavalent antimony compounds Certain aromatic diamidines have proved useful under special conditions as described below

The use of ethylstibamine (Neostibosan) has been highly successful except in the Sudan This drug is recommended for first courses in general It should be given slowly by vein as a 5 per cent solution in sterile distilled water The solution is relatively unstable and must be freshly prepared for each injection It should be used as soon as possible without boiling or heating The first dose for adults is 0 2 gm and subsequent doses are 0 3 gm Unless untoward effects appear doses should be given daily until a total of 3 0 to 5 0 gm has been administered Nausea and vomiting are the commonest side effects Dizziness cough abdominal and muscular pain diarrhea renal disturbances urticaria and increased bleeding are unusual toxic effects Increased fever is usually the result of the presence of pyrogens in the distilled water Anaphylactic shock has been reported in rare instances If agranulocytosis develops as it may rarely treatment should be interrupted until this condition has improved but should be resumed as soon as possible Otherwise it should rarely be necessary to interrupt chemotherapy completely though it is not infrequently wise to restrict drug administration to alternate days or to reduce the dosage when untoward effects appear Pentavalent antimony compounds which may be used instead of ethylstibamine include sodium antimony gluconate (Pentostam formerly designated Solustibosan) and stibamine glucoside (Neostam) These drugs are regarded as both less toxic and less effective than ethylstibamine but they possess the advantage that they can be given intramuscularly

Patients under treatment should be followed closely with special attention to the leukocyte count The response to therapy is sometimes dramatic sometimes slow Fever is usually absent after the first two weeks but may persist briefly after completion of treatment The leukocyte count is generally normal in three or four weeks Improvement in the erythrocyte count is heralded by a marked increase in reticulocytes It may take many weeks for erythrocytes and hemoglobin to become wholly normal Serum proteins take three to six months to reach normal values The spleen and liver often recede rapidly but in long standing cases the spleen may remain large for months Cure may follow a single course of therapy even though progress is slow The treatment outlined rarely fails entirely but 5 to 10 per cent of patients relapse Most relapses occur within two months but the interval is sometimes four or five months Patients should be followed for six months before being declared cured Relapses are usually marked by the return of fever followed by the characteristic picture The continued presence for a few weeks of Leishmania alone does not necessarily indicate that a relapse will occur but clinical suggestions of a relapse should be confirmed by demonstration of the parasite When the occurrence of a relapse is established another course of treatment should be given This may again consist of ethylstibamine in which case larger doses are desirable (up to 0 5 gm a day for twenty days) Such second courses have cured many patients Or recourse may be had to one of the newer drugs

The diamidines stilbamidine isethionate and pentamidine isethionate have given better results than pentavalent antimonials in the treatment of kala azar in the Sudan and in some resistant cases elsewhere although they have not been found more satisfactory in general These drugs have potentially great toxicity which calls for special care in their use In most areas they are best held in reserve for cases resistant to pentavalent antimonials Stilbamidine

nomonic The formol gel test and the antimony test which depend upon the presence of hyperglobulinemia and hypoalbuminemia are helpful in the Far East These tests however may be negative in the first few weeks of the disease and are positive in certain other diseases though rarely to the degree commonly seen in kala azar Actual measurement of serum globulin and albumin supplies data useful both in diagnosis and in following the course of treatment

The *formol gel test* is done by adding 1 or 2 drops of formalin to 1 ml of clear serum Complete opacity within twenty four hours constitutes a positive result Partial opacity is a doubtful result and a persistently clear serum is negative even though it gels

The *antimony test* consists in diluting serum ten times with distilled water and adding to 2 ml of diluted serum the same amount of 4 per cent solution of ethylstibamine (Neostibosan) in distilled water The materials are mixed by rotating the test tube between the palms A positive result is indicated by a heavy flocculent precipitate a doubtful one by mere clouding and a negative one by complete absence of precipitation

The diagnosis should always be confirmed by demonstration of the parasite Although L-D bodies are probably always present in the blood of active cases they are usually so difficult to find that reliance should not be placed on blood smears A small amount of tissue for examination should be obtained from one of the sites in which parasites are normally plentiful which include spleen liver sternal bone marrow lymph nodes and skin lesions The simpler procedures for obtaining the necessary material are aspiration of sternal bone marrow or enlarged lymph nodes and excision of lymph nodes or nodules The spleen has been shown however to be the most reliable source of diagnostic material Spleen puncture is commonly regarded as presenting serious danger although it has been done in thousands of cases in the Far East with only rare accidents The procedure is not free from risk but experience amply justifies its use with proper precautions when bone marrow or lymph node material is negative in a case in which kala azar is a reasonable possibility It is important that the spleen extend well below the costal margin and that the bleeding and clotting times be within normal limits The technique is described in detail by Most

The tissue obtained should be prepared with a Giemsa or Wright stain The parasites probably live mostly within other cells but since macrophages are often ruptured in making smears extracellular Leishman Donovan bodies are common in such preparations They should not be confused with platelets Several preparations should be persistently searched for parasites conforming to the description given previously

When prolonged study of smears is fruitless one can rely on cultures or if a suitable species is available on animal inoculation Both methods are highly successful The material used is generally the same as that for smears the leukocyte layer of 10 ml of centrifuged citrated blood may also be tried Cultures are made on rabbits blood agar medium (Nicolle Novy Mc Neal N N N) and are incubted at 22° C Special care must be taken throughout to maintain aseptic technique In one to four weeks actively motile leptomonad forms may be found on high power search of a sample mixed with a little saline solution on a slide The organisms are sometimes best found in the water of condensation Details should be studied in stained smears The usual laboratory animals are refractory to infection with Leishmania but several species of hamster are highly susceptible Intratesticular inoculation of rabbits has been successfully used for diagnostic purposes Complement fixation agglutination and skin sensitivity tests have been used but their practical value is uncertain

Differential Diagnosis In differential diagnosis various forms of leukemia have been the most frequent cause of confusion in the United States Hodgkin s disease and infectious mononucleosis have also been diagnosed here instead of kala azar Histoplasmosis which closely resembles kala azar in some instances can be separated only by close attention to the comparative characteristics of the parasites Many other diseases may superficially resemble kala azar notably malaria but also brucellosis typhoid fever bacterial endocarditis disseminated lupus tuberculosis Weil s disease relapsing fever and schistosomiasis In all these instances the separation must be made by close study of the history and clinical picture and by use of applicable laboratory tests

Prognosis In the absence of treatment about 75 per cent of patients die often with an intercurrent infection and usually within two or three years Spontaneous recovery has been observed in rare proved cases Good treatment ultimately cures

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is both more efficacious and more toxic than pentamidine It is essential that these drugs be used in freshly prepared solutions The action of light on solutions produces dangerous hepatotoxic compounds A number of immediate reactions to intravenous injection including circulatory collapse may occur especially with stilbamidine and particularly with rapid injection After a course of stilbamidine (sometimes months later) a peculiar neuropathy usually having a trigeminal distribution appears in some cases Stilbamidine must be given intravenously the daily dose being dissolved in 200 ml of sterile fluid For adults the first dose is 25 mg In the absence of untoward effects the dose is increased each day by 10 to 20 mg until the dose of 150 mg is reached The total amount in a course varies usually falling between 2 0 and 4 0 gm Pentamidine can be given intravenously in doses of 2 0 to 4 0 mg per kg of body weight dissolved in 200 ml of sterile fluid or it can be given intramuscularly in similar doses dissolved in 5 ml of sterile fluid The total dose for a course is from 2 0 to 4 0 gm

In rare cases several courses of treatment with proper doses of antimonial and diamidine drugs are unsuccessful In a few such instances in which the spleen remained large and firm splenectomy has been quickly followed by apparent cure This operation should be considered in such cases but it should not be done unless the patient has had more than one course of chemotherapy and it should also be followed by a full course of chemotherapy

Postkala azar dermal leishmaniasis is relatively refractory but the best available treatment is a full course of ethylstibamine as outlined for the visceral stage

Prevention The source of the infection should be attacked by treatment of patients and in areas where dogs are infected by suitable steps against such animals The sandfly vector should be attacked by removing the conditions in which they abound Cracks and dark corners in walls and floors rubbish and vegetation in and around houses should be eliminated DDT residual spray is effective Ordinary screens and sleeping nets do not exclude sandflies but sprayed thoroughly with DDT or impregnated with repellent they do constitute a barrier Sandflies bite mostly after sunset Clothing is protective except near openings A repellent such as dimethylphthalate applied to exposed skin keeps sandflies off for four to five hours

CUTANEOUS LEISHMANIASIS

(Oriental Sore)

Definition and Incidence This name is given to an infection which is characterized by cutaneous granulomas with a strong tendency to ulceration In cases classified under this heading the disease is limited to the skin there being no evidence of involvement of other parts of the body It was formerly known by many local names such as Aleppo boil Its distribution is focal but widespread with centers in western India southwestern Asiatic Russia Iran Iraq Turkey Arabia all countries bordering on the Mediterranean Sea Abyssinia the Sudan French Congo and Nigeria Similar cases occur throughout Central and South America but it is uncertain that they are distinct from mucocutaneous leishmaniasis A number of imported cases have been seen in the United States

Etiology and Pathology The disease is caused by protozoa of the genus Leishmania which are known as *Leishmania tropica* Many parasitologists agree that this parasite cannot be reliably distinguished from *Leishmania donovani* the characteristics of which were previously described Sandflies of the genus Phlebotomus have been shown to transmit the disease from person to person and this is believed to be the common method of transmission Animal reservoirs however are probably important They exist in the dog in many areas and in the gerbil (a small rodent) in Asiatic Russia The evidence indicates that this form of cutaneous leishmaniasis is transmitted by other species of sandflies than those responsible for the spread of kala azar Direct inoculation from a sore sometimes occurs but is rare The pathology is that of the local lesion The basic change is an infiltration of all the layers of the skin mainly by reticuloendothelial cells (macrophages) which behave as they do in kala azar The circulation is interfered with and necrosis occurs followed by ulceration granulation and with healing the proliferation of fibrous tissue The infection is usually followed by immunity at least to the same strain of *Leishmania tropica* but apparently not to kala azar

Symptoms The period from infection to manifest disease extends from a few weeks to two or three years Systemic symptoms are rare and consist only of transient slight fever and malaise The lesions are usually multiple sometimes solitary They are commonly located on exposed surfaces espe

cially the face ears neck backs of the hands and forearms The scalp palms and soles escape In its earliest stages the lesion takes the form of a small red papule which often itches A slight exudate gives rise to fine adherent scales The papule enlarges slowly until in the course of a month or two it is 1 to 3 cm in diameter A thick rupia like scab usually forms Necrosis ordinarily takes place in the center of this lesion resulting in the formation of a roughly circular ulcer with clear cut margins which bleeds easily Pyogenic infection is common at this stage The surrounding area is somewhat swollen and indurated In addition to this typical evolution the lesion may take various other forms The infection is characteristically indolent usually lasting a year or more but occasionally sores follow an abortive course Fairly large lesions heal slowly with the formation of a contracted scar which is often disfiguring

Diagnosis In endemic areas the diagnosis is often based on the clinical picture but the lesions may be confused with those of many other diseases including syphilis yaws tuberculosis leprosy and various mycoses The diagnosis should always be confirmed by the demonstration of *Leishmania tropica* which can usually be found without difficulty in stained smears or N N N cultures of material from early lesions In large lesions material for examination should be obtained by puncturing or scraping the cleaned edges It is useless to study the central exudate Skin sensitivity tests have been used but their value is uncertain

Treatment This form of leishmaniasis responds less satisfactorily to chemotherapy than kala azar Cure and healing often require several weeks Numerous agents have been used but there is no general agreement as to the best method of treatment On account of the relatively benign nature of the disease treatment is usually given by local applications or injections Among the agents so used with success are superficial radiation solid carbon dioxide and by local injection berberine sulfate (2 per cent solution) quinacrine hydrochloride (10 per cent) stibamine glucoside (Neostam) and other pentavalent antimony preparations (2 per cent) Local injections should consist of about 2 ml given in various points on the periphery of the lesion at weekly intervals Judicious debridement of large ulcers is recommended Secondary infection should be treated by the systemic administration of an appropriate antimicrobial drug The pentavalent antimony compounds used for kala azar are sometimes given intravenously for oriental sore but the results are not clearly superior to those following local treatment A somewhat less intensive course of one of these drugs than that recommended for kala azar is advisable when the lesions of oriental sore are numerous

Efforts to prevent this form of leishmaniasis should follow the lines laid down for kala azar In addition lesions should be protected so that sandflies and other insects do not have access to them In highly endemic areas advantage is taken of the immunity which usually follows infection to protect selected persons against disfigurement by artificial inoculation of living parasites in inconspicuous areas

AMERICAN MUCOCUTANEOUS LEISHMANIASIS

(Espundia and Other Local Names)

Definition and Incidence This form of leishmaniasis which is attributed to *Leishmania brasiliensis* resembles the oriental cutaneous type in that it is characterized by skin granulomas but in addition many cases show ulcerative lesions of the nose mouth and pharynx The infection is endemic in most if not all Central and South American countries and in the Yucatan peninsula (Mexico) It is especially common in forested areas It is considered to be distinct from kala azar which also occurs in certain parts of South America

Etiology and Pathology The disease is caused by Leishmania assigned to the genus *L brasiliensis* although the organisms cannot be reliably separated from those responsible for the other forms of human leishmaniasis Sandflies are capable of transmitting the infection The parasite has been recovered from dogs but dogs do not seem to be an important source of human disease The basic pathological changes are similar to those in oriental cutaneous leishmaniasis but in many cases the infection spreads regionally through local lymphatic or blood channels producing involvement of the naso oral mucosa and neighboring lymph nodes Visceral involvement resembling that of kala azar has recently been reported

Symptoms There are usually three or four skin lesions but often only one and rarely a large number located on exposed parts of the body In form the lesions often resemble those of oriental sore Ulceration

may not appear for months or even years and sometimes does not occur In the ab sence of ulcer formation the lesion may acquire a verrucose form In a few cases nodules are formed along lymphatics and regional lymph nodes are enlarged The incidence of mucosal lesions is variable in different areas but reaches 20 per cent in Brazil These lesions usually appear about a year after the skin lesions occasionally only many years later They begin as swell ings which ulcerate and slowly spread so that they may become extensive and cause serious destruction anywhere in the nose mouth or pharynx The infection is per sistent often lasting for many years if not for life in the absence of treatment Secondary infection of ulcerated areas is common and may be fatal Enlargement of liver and spleen with hyperglobulinemia has been described in a few cases

Diagnosis The diagnosis should always be based on the demonstration of the para site which is recoverable from the more recently invaded tissue of skin and mucosal lesions In many cases the organism can be found in material from regional lymph nodes and from the nasal mucosa even in the absence of mucosal lesions Appropri ate methods were described for kala azar

Treatment No standard plan is generally recognized but the use of both local and systemic therapy is recommended for most cases Local treatment of skin lesions should follow the lines suggested for ori ental cutaneous leishmaniasis For systemic treatment the standard intravenous course of a pentavalent antimonial used against kala azar deserves careful trial which it has not yet had Snapper has described the successful treatment of a patient with mucosal lesions by the use of a stilbami dine derivative The parenteral therapy most frequently used has consisted either of antimony and potassium tartrate or of stibophen (Fuadin) both given intrave nously Extensive mucosal lesions require much attention The persistence and pains used to secure and maintain cleanliness are more important than the particular drug applied locally Sodium perborate or boric acid solution may be used Systemic treat ment with a suitable antimicrobial drug should be given for concurrent infections Patients should be followed for a year to see that mucosal lesions do not develop or recur The prevention of this disease follows the recommendations given for kala azar and oriental cutaneous leishmaniasis

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Toxoplasmosis

Etiology *Toxoplasma gondii* probably a protozoon is a crescentic organism 4 to 6 μ long and 2 to 3 μ wide which causes acute chronic and asymptomic infections Toxo plasma infections have been reported from numerous birds and mammals Of im portance to man are infections of dogs cats pigeons chickens rats rabbits guinea pigs swine sheep and cattle Human toxo plasmosis is widespread in North South and Central America Europe Asia and Africa

Life Cycle *Toxoplasma gondii* lives intracellu larly in the reticuloendothelial system in paren chymal cells and extracellularly Large aggregations of parasites form pseudocysts in various or gans Reproduction is by longitudinal binary fis sion Except for transplacental transmission the mode of spread from man to man is unknown Transmission through respiratory droplets feces arthropods and uncooked infected pork have all been suggested with some experimental or epi demiological evidence

Morbid Anatomy In toxoplasma infection of in fants the organism is widely disseminated with inflammatory and necrotizing lesions in the heart lungs adrenals central nervous system eyes and striated muscles In infants who survive more than the first few days after birth the parasites dis appear from most sites and regression of lesions takes place except in the central nervous system and eyes The brain shows widespread changes consisting of meningoencephalomyelitis large areas of necrosis cyst formation and calcification The spinal cord may be similarly affected In adults the outstanding gross lesions at autopsy have been limited to the lungs and resemble those of inter stitial pneumonia of viral origin

Symptoms There are two types of disease produced in man by toxoplasma con genital and acquired Acute congenital in fections are characterized by hydrocephalus or microcephaly convulsions tremors twitchings contractions of the extremities paralysis opisthotonos microphthalmos

endophthalmos and nystagmoid movements Chorioretinitis is almost a constant feature of congenital toxoplasmosis The cerebrospinal fluid is xanthochromic contains an increased number of erythrocytes and mononuclear cells and has a high protein content Jaundice hepatosplenomegaly thrombocytopenia and purpura may be present Roentgenographic examination of the skull reveals small areas of calcium density Infants who survive the infection exhibit chronic hydrocephalus or microcephaly convulsions paraplegia speech defects and defective vision

The acquired infection assumes several forms In the acute disease there may be a maculopapular rash pneumonitis cough fever headache arthralgia myalgia lymphadenopathy conjunctivitis and myocardial involvement Subacute infections exhibit lymphadenopathy with or without fever There is a subclinical form in which the patient has no fever nor does he complain of lymph node enlargement but lymphadenopathy is discovered on physical examination Lymphocytosis of 50 to 70 per cent is common in acquired infections and atypical mononuclear cells consistent with infectious mononucleosis may be present Chorioretinitis and uveitis have been reported a number of times in acquired adult toxoplasmosis

Diagnosis The signs and symptoms of congenital toxoplasmosis are highly suggestive but the acquired infections are often mild and unsuspected The cerebrospinal fluid is xanthochromic contains an increased number of cells and has a high protein content Serological tests have been widely used as aids in diagnosis and are of greatest significance in congenital infections The dye test of Sabin and Feldman usually becomes positive early in the infection and persists for several years This test is based on the fact that toxoplasmas incubated in normal serum stain with methylene blue while those incubated in antibody-containing serum lose their affinity for the stain A toxoplasma complement fixation test is available In general the dye test becomes positive before the complement fixation test rises to a higher titer and remains positive after the complement fixation test has reverted to negative An intradermal test is available but as it is less specific than the other tests it is of limited clinical value

Prognosis Acute congenital toxoplasmosis is usually fatal and children surviving it are often incapacitated Acquired infections vary greatly depending upon the organs involved many are asymptomatic Mothers who give birth to toxoplasma infected children give birth subsequently to normal noninfected children

Treatment As the course of toxoplasmosis varies considerably and the lesions tend to spontaneous arrest it is difficult to evaluate the effects of chemotherapy Sulfonamides in conjunction with pyrimethamine (Daraprim) appear to be promising Successful results have been reported from the use of triple sulfonamide (equal parts of sulfadiazine sulfamerazine and sulfamethazine) in an initial dose of 3 0 gm followed by 1 0 gm every four hours in conjunction with pyremethamine 50 mg initially 25 mg six hours later then 25 mg daily This multiple-drug therapy was continued for fourteen days Adrenal corticosteroids are reported to be of value in acute exacerbations of chronic lesions

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Ciliate Infections

BALANTIDIASIS

Etiology Balantidiasis is an infection of the large intestine with *Balantidium coli* characterized by disturbances varying from a mild colitis to acute dysentery *B coli* is a large (100 by 60 μ) egg shaped ciliate containing a large kidney shaped macronucleus and a small micronucleus The trophozoites are the pathogenic stage and under unfavorable conditions they may produce a protective wall and become cysts

Morbid Anatomy The trophozoites invade the mucosa submucosa and muscularis chiefly of the cecum and upper portion of the large intestine and less commonly the small intestine in the area of the ileocecal valve Cytolytic enzymes and mechanical penetration are probably involved in the parasite s tissue invasion It feeds on erythrocytes leukocytes tissue fragments and intestinal debris

The early intestinal lesions consist of minute hemorrhages round cell infiltration and eosinophilia Multiplying trophozoites form small submucosal abscesses that break down into ulcers with undermined edges Intestinal perforation may occur It is believed by some that bacteria are necessary for the invasion of tissues by Balantidium The chronic lesions are frequently complicated by secondary bacterial invaders Although trophozoites have been found in mucosal blood vessels and lymphatics invasion of the liver or other organs has not been reported

Epidemiology Human infections with *B coli* have been reported from most areas of the world Infection of hogs with Balantidium is very prevalent and this form is considered to be the source of human infection The monkey chimpanzee rat and guinea pig harbor species of Balantidium indistinguishable from the human form Shookhoff reported twenty infections among Puerto Ricans the majority of whom were children Eighteen of twenty of his patients reported close contact with hogs Association with hogs by only 25 to 50 per cent of the patients of other studies suggests other sources of infection Institutional infections indicate person to-person transfer Transmission is through the ingestion of cysts in water and food contaminated by infected feces Handling hogs in slaughter houses and on farms may lead to infection

Symptoms In Shookhoff s group of twenty patients only ten had symptoms referable to the infection the remainder appeared to be asymptomatic carriers Of those with symptoms eight had diarrhea four had abdominal pain and two had anorexia one child of three years of age had diarrhea for two years Anemia and slight leukocytosis with eosinophilia were present in several of this group In severe infections there is dysentery with six to fifteen bowel movements per day abdominal pain nausea vomiting headache weakness and fever Strong collected 111 severe cases and found a mortality rate of 29 per cent The mortality rate in 57 mild infections was 7 per cent Fatal infections show extensive multiple diffuse ulceration gangrene and perforation

Diagnosis The clinical picture of balantidiasis may resemble that of intestinal amebiasis The diagnosis is made by finding the trophozoites or cysts in the patient s stool The large size of the trophozoite and its constant movement "ploughing through the liquid fecal film make it easy to find

Treatment Diodoquin carbarsone and the tetracycline drugs are the agents of greatest therapeutic value in balantidiasis Their relative efficacy has not been determined in large enough groups of patients to be significant Diodoquin because of its efficacy safety and cost is to be preferred A dose of 0 65 gm three times a day for twenty one days is given to all patients ten years of age or older Children one to four years of age are given 0 21 gm three times a day and those five to nine years of age 0 42 gm three times a day for twenty one days Secondary bacterial infection should be treated with a tetracycline or sulfonamide Supportive therapy consisting of fluids vitamins adequate diet and iron is indicated in severe and chronic infection

Prevention The prevention of balantidiasis consists in care not to contaminate food or drink with human or porcine feces The usual precautions against such transmission should be taken handwashing proper disposal of excreta treatment of carriers and health education

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METAZOAN INFECTIONS

Metazoa are invertebrate animals made up of many cells which in aggregates are usually specialized into tissues and organs performing particular but coordinated functions of the entire organism In this respect metazoa differ from protozoa the one-celled organisms in which all the functions are performed by specialized parts of the protoplasm within a single cell unit The parasitic metazoa are found primarily within the following invertebrate groups

A Platyhelminthes (flatworms)
  1 Trematoda (flukes)
  2 Cestoda (tapeworms)
B Nemathelminthes (roundworms)
C Hirudinea (leeches)
D Arthropoda (insects and their relatives)

HAROLD W BROWN

Table 1 Prevalence of Helminth Infections in Man

PARASITE	SOURCE OF INFECTION	UNITED STATES CANADA	WORLD-WIDE
NEMATHELMINTHES (ROUNDWORMS)			
Trichinella spiralis	Pork	21 100 000	27 800 000
Enterobius vermicularis	Human feces	18 000 000	208 800 000
Hookworm	Human feces	1 800 000	456 800 000
Ascaris lumbricoides	Human feces	3 000 000	644 400 000
Trichuris trichiura	Human feces	400 000	355 100 000
Strongyloides stercoralis	Human feces	400 000	34 900 000
Trichostrongylus spp	Human feces	*	5,500 000
Dracunculus medinensis	Cyclops	—	48 300 000
Onchocerca volvulus	Black fly	—	19 800 000
Mansonella ozardi	Culicoides	—	7 000 000
Acanthocheilonema perstans	Culicoides	—	27 000 000
Loa loa	Mango fly	—	13 000 000
Wuchereria bancrofti and *malayi*	Mosquitoes	—	189 000 000
PLATYHELMINTHES (FLATWORMS)			
A CESTODA (TAPEWORMS)			
Taenia saginata	Beef	100 000	38 900 000
Taenia solium	Pork		2 500 000
Echinococcus granulosus	Dog feces		*
Hymenolepis nana	Human feces	100 000	20 200 000
Diphyllobothrium latum	Fish	*	10 400 000
B TREMATODA (FLUKES)			
Clonorchis sinensis	Fish	—	19 000 000
Opisthorchis felineus	Fish	—	1 100 000
Fasciolopsis buski	Water nuts	—	10 000 000
Paragonimus westermani	Crabs—crayfish	—	3 200 000
Schistosoma japonicum	Water through skin	—	46 000 000
Schistosoma haematobium	Water through skin	—	39,200 000
Schistosoma mansoni	Water through skin	—	29 200 000
Total infections		44 900 000	2,257 100 000
Population		143 500 000	2,166 800 000
Per cent infections of population		31	104 2

* Represents less than 100 000 infections
(From Stoll N R J Parasit 33 1 1947)

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The Platyhelminthes (Flatworms)

Trematode or Fluke Infections

(*Trematodiasis*)

Trematodiasis is an infection with the species Trematoda or so called flukes Most flukes infecting man are flat and often leaf like with the mouth at the anterior end surrounded by a muscular sucker and a second ventral sucker for attachment to the host Except for the schistosomes the flukes infecting man are hermaphroditic The flukes have a complicated life cycle in addition to man who harbors the adult a snail intermediate host is always involved Infection of man takes place by direct penetration of the cercariae (schistosomiasis) or by the ingestion of infected fish crustaceans or fresh water plants which harbor the metacercariae

INTESTINAL TREMATODES

FASCIOLOPSIS BUSKI

Etiology *Fasciolopsis buski* is a large intestinal trematode which man shares with the hog It is an important parasite of man in China the Bengal areas of India and East Pakistan Thailand Malaya and neighboring areas

Life Cycle The adult worms which are hermaphroditic average 3 cm in length and 1 2 cm in breadth They daily pass thousands of large operculate eggs which are passed in the feces and mature only in water After several weeks of development a ciliated free swimming miracidium hatches from the egg and actively penetrates its appropriate snail host A multiplicative cycle takes place in the snail and cercariae are shed which encyst on certain water plants of the genera Trapa and Eliocharis which when eaten serve as the source of human infection Large numbers of encysted cercariae metacercariae may be present on the outer layers of water nuts When eaten raw the nuts are peeled with the teeth freeing the metacercariae which are swallowed and mature into adult worms in three months

Symptoms Fasciolopsis attaches by means of its ventral sucker to the mucosa of the upper small intestines where it feeds on the intestinal contents Localized foci of inflammation ulcerations and abscesses occur at the site of attachment Erosion of capillaries may result in bleeding Epigastric pain of varying severity occurs especially in the morning Food frequently allays the pain but may lead to additional infection in the field through the eating of raw water nuts Severe diarrhea accompanied by nausea and vomiting may alternate with constipation

Several thousand worms may be harbored by heavily infected patients Severe and fatal infections are accompanied by a marked edema ascites and anasarca The edema may be due to the absorption of toxic metabolites of the parasite Anemia is present in some patients There is a leukocytosis in approximately one half of the patients however leukopenia and lymphocytosis may be present Eosinophilia is common and may reach 34 per cent

Diagnosis The symptoms of this form of fluke infection (fasciolopsiasis) are sufficiently characteristic when encountered in endemic areas to suggest a stool examination As a relatively large number of eggs are passed by each worm even light infection should be detected The eggs may be confused with those of *Fasciola hepatica*

Prognosis In severe infections with extensive anasarca the prognosis is grave especially if anthelmintics are not administered

Treatment Hexylresorcinol ("Crystoids Anthelmintic) is effective in the treatment of fasciolopsiasis The adult dose is 1 0 gm and children are given 0 1 gm per year of age up to ten years A light or liquid meal should be taken the evening before treatment The drug is administered the following morning on an empty stomach and no food should be taken for four hours A single treatment cures 54 per cent of the infections and greatly reduces the worm burden of the remainder Tetrachlorethylene is also recommended for this infection Patients recover quickly following therapy

Prevention The prevention of infection with the fluke *Fasciolopsis buski* consists of thorough cooking of vegetables which have been exposed to the infection Infected persons should be treated and in areas where the infection rate is high mass treatment should be undertaken Destruction of the snails by the use of copper sulfate is practicable in small plots where the water nuts are grown Prolonged storage of night soil with slaked lime will destroy the ova of Fasciolopsis

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OTHER INTESTINAL TREMATODES

Trematodes of various mammals and birds infect people who eat raw or inadequately cooked fish which harbor the metacercariae *Heterophyes heterophyes* or *Metagonimus yokogawai* The adult worms are 1 0 to 2 5 mm in length and live in the mucosa of the small intestine Large numbers of these minute parasites cause inflammation of the intestine diarrhea and abdominal discomfort Occasionally heterophyid eggs gain access to the mesenteric lymphatics and the blood stream and are carried to the myocardium brain spinal cord and kidneys where they cause considerable damage The eggs of these trematodes which are found in the stool are small operculate and may be confused with those of Clonorchis

Treatment with tetrachlorethylene (as for hookworm) or hexylresorcinol (as for ascariasis) is recommended although the habitat of the worms makes them difficult to dislodge *Prevention* consists in eating only thoroughly cooked fish

A number of Echinostomatidae characterized by spines about the anterior sucker have been reported as producing disease in man although they are normally parasites of birds and mammals other than man Infection is acquired by eating a variety of small animals raw such as snails fresh water fish and molluscs The adult worms live in the small intestine of man and those of the genera Echinostoma Echinochasmus and Paryphostomum are reported to cause diarrhea and abdominal pain Therapy with tetrachlorethylene removes large numbers of the worms

HEPATIC TREMATODES

CLONORCHIS SINENSIS

(Liver Fluke)

Clonorchis is widespread in the Far East including China Indo China Korea and Japan It is common in dogs and cats in these areas but human infection is limited to areas where fish is eaten raw pickled or smoked

Life Cycle The adult worms are 10 to 25 mm in length and 3 to 5 mm wide They live in the bile ducts of the liver and feed upon its secretions They live as long as twenty five years Eggs passed in the bile duct find their way out of the host in the feces Susceptible snails ingest the ova and after larval development and multiplication free swimming cercariae emerge which encyst on fresh water cyprinoid fishes Man and mammal become infected by eating raw or partially cooked fish The metacercariae are digested free of the fish flesh and are liberated in the duodenum They migrate by way of the ampulla of Vater to the bile ducts of the liver becoming adults in one month

Pathology and Symptomatology The distal bile ducts inhabited by Clonorchis are irritated by the parasite and its toxic secretions The biliary epithelium undergoes an extensive adenomatous proliferation accompanied by a thickening of the duct walls The dilated portions of the bile ducts are filled with worms and a brownish fluid containing eggs and leukocytes Bacterial infection may occur and lead to ulceration Periportal and central fibrosis and fatty changes in the parenchymal cells are frequently encountered at autopsy As many as 21 000 worms have been found in a heavily infected liver They also invade the pancreas

Since the worms are acquired over a long period and since they live twenty to twenty five years the disease usually has an insidious onset and is chronic Indigestion characterized by epigastric pain eructation of gas and nausea are early symptoms During the early stages of the infection a leukocytosis and marked eosinophilia are often present but they recede as the infection becomes chronic The liver is enlarged and tender and may be accompanied by a slight icterus In heavy infections diarrhea persistent liver enlargement edema ascites and cachexia develop Systemic disease toxicity with tachycardia palpitation vertigo tremor and mental depression have been reported

Diagnosis Patients from endemic areas with a history of eating raw fish with or without symptoms should have a stool examination The small operculate egg

resembles those of several other hepatic and intestinal flukes Severe advanced infections must be differentiated from other forms of hepatic cirrhosis malignancy amebic hepatitis and echinococcus cyst

Treatment The therapy of clonorchiasis is not very satisfactory Gentian violet given orally relieves symptoms in acute clonorchiasis and may cure early light infections It reduces the number of worms in chronic infections The adult dose of gentian violet is 65 mg three times a day with meals for thirty days Repeated courses of therapy are frequently required Recently acquired light infections may respond to potassium antimony tartrate Chloroquine 0 5 gm three times a day for two to three weeks relieves symptoms reduces the numbers of eggs found in the stool in most infections and in approximately one third of the patients results in a cure

Prevention The prevention of infection with this liver fluke consists of thorough cooking of all fresh water fish from endemic areas when preparing them for eating

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FASCIOLA HEPATICA

(*Sheep Liver Fluke*)

Etiology *Fasciola hepatica* an accidental parasite of man is primarily a parasite of sheep and other herbivorous animals The sheep liver fluke causing the disease liver rot has a world wide distribution and human infections though not numerous are similarly widespread About one third of the reported human infections are from Cuba Although sheep in the United States are infected and human infections could arise there all persons infected thus far have also visited other endemic areas *F gigantica* of cattle is an infrequent parasite of man

Life Cycle The adult worms 30 mm in length and 13 mm wide live in the bile ducts liver parenchyma and gallbladder Their large operculate eggs pass with the bile into the intestine and are evacuated in the feces The miracidium which hatches from the egg invades a lymneid snail where development and multiplication take place The cercariae which emerge from the snail crawl up on moist vegetation and encyst The encysted metacercariae are ingested with grass Man is probably infected through eating infected watercress or drinking water that contains detached cysts When they reach the upper small intestine the metacercariae are liberated and burrow through the intestinal wall by way of the peritoneal cavity they enter the liver where they mature The migrating larvae sometimes go astray and are trapped in various tissues giving rise to ectopic infections

Pathology and Symptomatology In animals the migration of the immature worm through Glisson s capsule and the liver parenchyma may cause considerable damage The mechanical and toxic action of the parasites leads to hyperplasia of the biliary epithelium with adenomatous cystic dilatation There is a marked increase in connective tissue of the ducts with portal cirrhosis and pressure necrosis of the parenchyma

The migration of the young worms through the hepatic tissues gives rise to an enlarged painful liver and fever The adult worms cause hepatic pain and tenderness abdominal rigidity fever and diarrhea Leukocytosis and marked eosinophilia are present Acute cholecystitis obstruction of the common bile duct and jaundice have been reported In severe infections the patient may exhibit anemia weight loss and a profound toxicity due to the absorption of toxic products of the worms The presence of the worm in ectopic locations such as the intestinal wall abdominal wall muscles of the neck brain or eye gives rise to localized symptoms The ingestion of infected raw sheep and goat liver may lead to halzoun (*i e* suffocation) due to lodgement of the adult worm in the pharynx or larynx of man

Diagnosis The history of hepatic pain eosinophilia and eating watercress is suggestive of hepatic infection with a fluke and should lead to an examination of the stool for Fasciola eggs

Prognosis The prognosis of Fasciola disease is good in light infections and poor in heavy infections with severe liver involvement

Treatment Emetine hydrochloride 0 04 gm daily for a total dose of 5 mg per kg of body weight is effective Carbon tetrachloride is effective but dangerous in the presence of liver damage Ectopic flukes should be removed surgically

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OTHER HEPATIC TREMATODES

Opisthorchis felineus *O viverrini* and *Dicrocoelium dendriticum* are liver flukes of man which may produce a clinical picture similar to that of Clonorchis *O felineus* is found in man in East Prussia Poland the U S S R and the Far East *O viverrini* is prevalent in Thailand Both species are common in cats and dogs in endemic areas Man acquires the infection by eating raw fish harboring the metacercaria stage *D dendriticum* has a cosmopolitan distribution in sheep where it lives in the liver Man becomes infected accidentally by ingesting the ant intermediate host Ingestion of sheep liver harboring this parasite results in the eggs being present in man s stool temporarily an example of spurious parasitism *Treatment* of these infections is similar to that of clonorchiasis

PARAGONIMIASIS

(*Lung Fluke*)

Etiology The adult lung fluke *Paragonimus westermani* is thick reddish brown 8 to 12 mm in length and 4 to 6 mm in width and typically lives encapsulated in the lungs The infection in man is widespread in the Orient especially in Japan Taiwan Korea China the Philippines and Indonesia A few infections have been reported from Africa and South America Only one human infection has been reported from the United States although the adult parasite is present among mammals and the larval form in crayfish

Life Cycle The normal site of the adult worm is in the lungs and the eggs are found in the sputum as sputum is swallowed the eggs may appear in the feces The eggs develop in fresh water The liberated miracidium enters a suitable species of snail in which development and multiplication takes place Cercariae emerge from the snail and enter the soft tissues of fresh water crabs and crayfish where they encyst Man dogs cats and many other mammals acquire infections from eating uncooked crabs or crayfish harboring the cysts with metacercariae Infection may be acquired from drinking water which contains detached cysts The metacercariae excyst in the duodenum migrate through the intestinal wall traverse the peritoneal cavity burrow through the diaphragm and enter the lungs where they grow to maturity in eight to nine weeks The eggs find their way into the sputum through ruptured bronchi

Morbid Anatomy An eosinophilic neutrophylic infiltration surrounds the growing worm in the lung and gradually a thick fibrous capsule is formed The cysts are 6 to 10 mm in diameter and are surrounded by congested edematous tissue The cyst contains one or more worms in a brownish necrotic gelatinous exudate containing typical operculate eggs The cysts may suppurate ulcerate and resemble tuberculous lesions Aberrant worms wander into various parts of the body and may be found in the abdominal cavity and abdominal wall liver spleen mesenteric lymph nodes omentum intestinal wall prostate pleural cavity pericardium brain orbital cavity muscle skin and testes

Symptomatology The pulmonary disease produced by this lung fluke progresses slowly and resembles tuberculosis in many respects The patients have a cough most pronounced on rising in the morning sputum which is blood stained rusty or purulent occasional attacks of hemoptysis and chest pains Pleurisy is often present Dyspnea fever and anorexia are present in heavy infections There may be slight anemia leukocytosis and eosinophilia The erythrocyte sedimentation rate is slightly increased The physical signs may suggest tuberculosis pneumonia or bronchiectasis A high eosinophilia is often found in the pleural fluid Abdominal infection is characterized by abdominal pain of varying intensity and sites depending upon the organ involved Tenderness and rigidity of the abdomen may be present and with ulceration of the intestine blood and ova may be found in the stool

Cerebral infection produces jacksonian epilepsy with varying degrees of hemiplegia monoplegia visual disturbances and paresis An increased cell count in the cerebrospinal fluid with as high as 60 per cent eosinophils has been reported

Diagnosis In endemic areas the clinical symptoms of pulmonary paragonimiasis are suggestive but it must be remembered that in these areas tuberculosis is also very common and that the patient may have both infections Opinions differ as to the value of chest roentgenography in differential diagnosis Nodules up to 4 0 cm in diameter are present The diagnosis is definitely established by finding the eggs in the sputum Eggs in the feces may originate in swallowed sputum or in intestinal lesions Worms lodged in various organs such as the brain cannot be diagnosed by sputum or stool examination A concomitant pulmonary infection may be present A diagnosis of extrapulmonary infection may be made by the complement fixation test Subcutaneous creeping tumors are strongly suggestive of the disease in patients from endemic areas

Prognosis As the majority of worms live approximately six years in the absence of reinfection the disease gradually subsides on the death of the worms The prognosis is good in light or moderate infections In heavy infections those with superimposed pyogenic or tuberculous infections or cerebral involvement the prognosis is unfavorable

Treatment No effective specific therapy is available at present Emetine hydro chloride 0 065 gm intramuscularly daily for twelve days temporarily reduces the egg production of the worms Sulfonamide ad ministered concurrently appears to be of value Tartar emetic as given for schisto somiasis temporarily relieves pulmonary symptoms

Recently Chung and Hou reported clini cal and parasitological cures with chloro quine which was administered over a period of 93 to 231 days The total dosage em ployed varied from 26 8 to 85 7 gm

Infections of the brain can be cured only by surgery

Prevention The prevention of pulmonary paragonimiasis consists in eating only thor oughly cooked crayfish and crabs Salting pickling or soaking in rice wine is not suf ficient to kill the metacercariae Infected sputum and feces must be disinfected or kept from water

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Schistosomiasis

(*Bilharziasis*)

Etiology Schistosomiasis is a chronic dis ease caused by the eggs and the adult schistosomes or blood flukes *Schistosoma mansoni* and *S japonicum* live in the small venules of the intestine and *S haematobium* in the vesical and pelvic plexuses The mi gration of the eggs through the intestine and urinary bladder and their accumulation in the liver lungs and central nervous sys tem produce the characteristic syndrome

Life Cycle The delicate adult worms which are 0 6 to 2 5 cm in length reside in pairs the female lying in the gynecophoric canal of the male De pending upon the species of worm from 300 to 3500 eggs are passed daily into the venules A larval form miracidium develops within the egg its lytic enzymes and the contraction of the venule rupture the wall of the venule liberating the egg into the perivascular tissues of the intestine or urinary bladder The eggs effect a passage into the lumen of these organs and are evacuated in the feces or the urine On contact with fresh water the miracidia hatch from the eggs and swim about until they find an appropriate snail which they penetrate After two generations of development and multiplication within the snail the forked tailed cercarial progeny emerge During bathing swimming working or washing clothes the skin of man comes in contact with free swimming cer cariae which become attached and burrow down to the peripheral capillary bed as the surface film of water drains off If ingested with water the cercariae penetrate the mucous membrane of the mouth and throat The cercariae are transported through the afferent blood to the right heart and lungs They squeeze through the pulmonary capil laries and are carried into the systemic circulation Usually only those which get into the mesenteric arteries and pass through to the portal vessels sur vive Within the intrahepatic portion of the portal system the successful blood fluke larvae feed and rapidly grow Approximately 20 days after skin exposure the adolescent worms migrate against the portal blood flow into the mesenteric vesical and pelvic venules

Geographical Distribution *S mansoni* has an ex tensive distribution in Egypt Africa Madagascar Yemen the West Indies and the northern part of South America *S japonicum* is found in Central and South China Japan the Philippines and Cele-bes It is found in domestic and wild mammals in Taiwan but the strain does not develop to maturity in man *S haematobium* is very prevalent in Egypt and throughout Africa It is present in areas of the Near East Middle East Madagascar Portugal and a small area near Bombay India It is estimated that 114 000 000 persons are infected with schisto-somes Next to malaria it is man s most serious parasitic infection

INTESTINAL SCHISTOSOMIASIS

Symptoms Intestinal schistosomiasis is caused either by *S mansoni* which lives primarily in the venules of the large in testine and to a lesser extent in those of the ileum or by *S japonicum* which in habits the venules of the small intestine and also the large intestine The interval between infection and the onset of the acute generalized symptoms is approxi mately forty days in *S mansoni* infections and twenty eight to thirty five days in *S japonicum* infections Eggs first appear in in the stool at about the same time Symp toms may be absent very mild or may not appear for years in light infections in which there are relatively few eggs pro-duced to injure the host The adults live up to twenty five years

The infection may be divided clinically into three stages (1) incubational the period of migration and maturation of the growing worms (2) acute the period of egg laying and the escape of eggs into the lumen of the intestine and bladder (3) chronic the period of tissue fibrosis when eggs are trapped in the tissues

The incubation period is initiated by the

penetration of the skin by cercariae which may produce a transient pruritus and rash During the invasion of the liver and other organs by the immature worms petechial hemorrhages and foci of eosinophilic and leukocytic infiltration are produced Toxic and allergic reactions may cause urticaria subcutaneous edema asthmatic attacks leukocytosis and marked eosinophilia Toward the end of the incubation period the liver becomes enlarged and tender and there are abdominal discomfort fever sweating chilliness and sometimes diarrhea

With the initiation of egg laying the acute stage begins In the normal cycle the eggs work their way through the intestinal wall and escape in the feces when numerous they are accompanied by blood and necrotic tissue cells Many eggs are swept back into the blood stream

Autopsy of 110 persons infected with *S mansoni* revealed eggs in the following organs liver 20 per cent gallbladder 4 per cent lungs 24 per cent pancreas 5 per cent stomach 11 per cent small intestine 16 per cent cecum 23 per cent appendix 8 per cent ascending colon 29 per cent transverse colon 36 per cent descending colon 38 per cent rectum 44 per cent suprarenal gland 2 per cent mesenteric lymph nodes 2 per cent spleen 2 per cent urinary bladder 14 per cent vagina 19 per cent cervix 6 per cent uterus 21 per cent kidney 2 per cent ureters 5 per cent prostate 7 per cent and testes 6 per cent

Abdominal tenderness hepatitis anorexia fever headache myalgia dysentery weight loss leukocytosis and eosinophilia are characteristic of intestinal schistosomiasis A macrocytic hypochronic anemia and an increased erythrocyte sedimentation rate are often present Liver function tests are altered and blood gamma globulin is increased The acute stage lasts three to four months and of course it more severe in heavy infections and in *S japonicum* infections because of the larger number of eggs produced by this species

The chronic stage of the disease may develop in eighteen months in heavy infections and as late as twenty five years in light *S mansoni* infections The numerous eggs in transit through the intestinal wall and those trapped in it produce multiple foci of inflammatory reaction with pseudotubercle formation abscesses and ulceration These chronic inflammatory changes gradually lead to fibrosis Eggs become imbedded in the appendix and may cause appendicitis The deposition of eggs in the liver likewise produces an inflammatory reaction in the form of multiple small abscesses and pseudotubercles

The liver is enlarged in the acute stage of the disease but as the infection becomes chronic the liver recedes in size and although usually slightly enlarged may become subnormal in size The liver cells are atrophied and there is a periportal cirrhosis Although the cirrhosis of the liver may be extreme especially in *S japonicum* infections interference with bile flow rarely occurs Marked ascites may develop and dilated abdominal thoracic and esophageal veins are often present The cephalin cholesterol flocculation test may become significantly positive early in the infection and as the disease progresses this test is usually positive The thymol turbidity test is also positive especially late in the disease The spleen enlarges because of the tissue reaction to the eggs to pigment and to portal passive congestion

Depending upon the intensity and duration of the chronic infection the patient may have a colitis of varying degrees with the formation of polyps Headache malaise irregular slight fever diarrhea and abdominal pain are common The appetite becomes poor and the patient loses weight Leukopenia develops with anemia and the eosinophilia often persists but is not as marked as during the acute stage of the disease There is a drop in the erythrocyte sedimentation rate This stage may be prolonged for years and the patient may die of pneumonia or other infections or rupture of esophageal varices

Eggs occasionally pass into the systemic circulation and are filtered out in the brain or spinal cord producing various nervous disorders The symptoms encountered are headache disorientation coma aphasia amnesia confusion paraplegia spasticity altered reflexes incontinence cranial nerve involvement and jacksonian epilepsy

Secondary pulmonary schistosomiasis due to embolic eggs and occasionally adult worms in the lungs is very common although not usually serious Dyspnea and moist rales may be present Heavily infected patients may show signs of pulmonary hypertension and cardiac insufficiency

There appears to be little or no relationship of schistosomiasis to malignancy of the intestine or liver Carcinoma of the intestine has been ascribed to *S japonicum* but data on its relative prevalence in endemic and uninfected areas are not available Papillomatous and benign tumors are not uncommon among patients with intestinal schistosomiasis

Diagnosis Patients from an endemic area with a history of intestinal disease hepatic

Treatment No effective specific therapy is available at present Emetine hydro chloride 0 065 gm intramuscularly daily for twelve days temporarily reduces the egg production of the worms Sulfonamide ad ministered concurrently appears to be of value Tartar emetic as given for schisto somiasis temporarily relieves pulmonary symptoms

Recently Chung and Hou reported clini cal and parasitological cures with chloro quine which was administered over a period of 93 to 231 days The total dosage em ployed varied from 26 8 to 85 7 gm

Infections of the brain can be cured only by surgery

Prevention The prevention of pulmonary paragonimiasis consists in eating only thor oughly cooked crayfish and crabs Salting pickling or soaking in rice wine is not suf ficient to kill the metacercariae Infected sputum and feces must be disinfected or kept from water

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Schistosomiasis

(*Bilharziasis*)

Etiology Schistosomiasis is a chronic dis ease caused by the eggs and the adult schistosomes or blood flukes *Schistosoma mansoni* and *S japonicum* live in the small venules of the intestine and *S haematobium* in the vesical and pelvic plexuses The mi gration of the eggs through the intestine and urinary bladder and their accumulation in the liver lungs and central nervous sys tem produce the characteristic syndrome

Life Cycle The delicate adult worms which are 0 6 to 2 5 cm in length reside in pairs the female lying in the gynecophoric canal of the male De pending upon the species of worm from 300 to 3500 eggs are passed daily into the venules A larval form miracidium develops within the egg its lytic enzymes and the contraction of the venule rupture the wall of the venule liberating the egg into the perivascular tissues of the intestine or urinary bladder The eggs effect a passage into the lumen of these organs and are evacuated in the feces or the urine On contact with fresh water the miracidia hatch from the eggs and swim about until they find an appropriate snail which they penetrate After two generations of development and multiplication within the snail the forked tailed cercarial progeny emerge During bathing swimming working or washing clothes the skin of man comes in contact with free swimming cer cariae which become attached and burrow down to the peripheral capillary bed as the surface film of water drains off If ingested with water the cercariae penetrate the mucous membrane of the mouth and throat The cercariae are transported through the afferent blood to the right heart and lungs They squeeze through the pulmonary capil laries and are carried into the systemic circulation. Usually only those which get into the mesenteric arteries and pass through to the portal vessels sur vive Within the intrahepatic portion of the portal system the successful blood fluke larvae feed and rapidly grow Approximately 20 days after skin exposure the adolescent worms migrate against the portal blood flow into the mesenteric vesical and pelvic venules

Geographical Distribution *S mansoni* has an ex tensive distribution in Egypt Africa Madagascar Yemen the West Indies and the northern part of South America *S japonicum* is found in Central and South China Japan the Philippines and Cele-bes It is found in domestic and wild mammals in Taiwan but the strain does not develop to maturity in man *S haematobium* is very prevalent in Egypt and throughout Africa It is present in areas of the Near East Middle East Madagascar Portugal and a small area near Bombay India It is estimated that 114 000 000 persons are infected with schisto-somes Next to malaria it is man s most serious parasitic infection

INTESTINAL SCHISTOSOMIASIS

Symptoms Intestinal schistosomiasis is caused either by *S mansoni* which lives primarily in the venules of the large in testine and to a lesser extent in those of the ileum or by *S japonicum* which in habits the venules of the small intestine and also the large intestine The interval between infection and the onset of the acute generalized symptoms is approxi mately forty days in *S mansoni* infections and twenty-eight to thirty five days in *S japonicum* infections Eggs first appear in in the stool at about the same time Symp-toms may be absent very mild or may not appear for years in light infections in which there are relatively few eggs pro-duced to injure the host The adults live up to twenty five years

The infection may be divided clinically into three stages (1) incubational the period of migration and maturation of the growing worms (2) acute the period of egg laying and the escape of eggs into the lumen of the intestine and bladder (3) chronic the period of tissue fibrosis when eggs are trapped in the tissues

The incubation period is initiated by the

surfaces become inflamed painful micturi tion and frequency begin and mucus and pus are found in the urine Daily tempera ture elevation sweating malaise weakness and dull pain in the suprapubic region oc cur The leukocyte count is increased and there is usually a marked eosinophilia There is a progressive cystitis with ascending sec ondary infection of the ureters and kid neys and hydronephrosis Urinary fistulas of the scrotum perineum and adjacent areas are common A few patients show intestinal and rectal involvement Liver in volvement although not less frequent is much less severe than in *S japonicum* and *S mansoni* infection Pulmonary schisto somiasis however is not uncommon and the presence of the eggs produces paren chymatous and arterial lesions Extensive vascular arteritis and obliteration may cause death from cardiac failure Death however is usually due to anemia emacia tion exhaustion or secondary infection Vesical carcinoma is common in Egypt where schistosomiasis haematobium is highly endemic There appears to be a causal relationship since epithelioma is several times more frequent in patients with vesical schistosomiasis than in un infected persons The malignancy occurs relatively early in life and is reported in persons in the ten to twenty year age group the majority being less than forty years of age

Autopsy of a series of patients harboring *S haematobium* revealed eggs in the following organs urinary bladder 80 per cent ureters 69 per cent kidney 46 per cent vagina 81 per cent cervix 75 per cent uterus 79 per cent fallopian tubes 12 per cent ovaries 67 per cent prostate 55 per cent testes 34 per cent liver 43 per cent gall bladder 38 per cent pancreas 35 per cent stomach 32 per cent small intestine 34 per cent cecum 54 per cent appendix 60 per cent ascending colon 66 per cent transverse colon 73 per cent descend ing colon 65 per cent rectum 75 per cent supra renal gland 26 per cent mesenteric lymph nodes 32 per cent spleen 34 per cent

When large numbers of eggs are deposited in these various organs and tissues symptoms may be produced

Diagnosis Hematuria cystitis urinary calculi and other vesical symptoms in a patient from an endemic area are sugges tive Specific diagnosis consists in the re covery of eggs from the sediment which settles out at the bottom of a urinalysis glass into which the patient has voided Eggs will also be found in the stool if an intestinal infection is present Cystoscopic examination may reveal hemorrhagic papules sandy patches and papillomata Biopsy specimens of these areas will con tain eggs Roentgenographic examination will demonstrate calcified areas or shadows when large numbers of eggs have become calcified in the tissues Intravenous pyelog raphy is useful in demonstrating com plications

Prognosis The prognosis of vesical schistosomiasis is good except in the late ulcerative stages because *S haematobium* is relatively susceptible to chemotherapy Patients with chronic severe infections and superimposed septic infections especially the old and debilitated have a poor prog nosis

Treatment Treatment consists in the ad ministration of antimony compounds as recommended for intestinal schistosomiasis Intensive intravenous therapy employing relatively large amounts of sodium anti mony tartrate over a period of forty-eight hours is effective However the frequency of severe toxic reactions limits the useful ness of this therapeutic regimen The thioxanthone Miracil D or Nilodin ad ministered orally has been used in *S haematobium* infections with considerable success As it acts chiefly upon the repro ductive organs of the parasite apparently cured patients frequently relapse Anti biotics are indicated for secondary bacterial infection

Prevention Sanitary disposal of human feces and urine is essential for the control of schisto omiasis The economic need for night soil for fertilizer in the Orient and the religious practice of ablution in Moslem countries are complicating factors Popula tions must be educated to use sanitary toilet facilities and to avoid contact with infected water Safe facilities for bathing and wash ing of clothes must be provided Control of snails with copper sulfate sodium penta chlorphenate and dinitro-o-cyclohexylphenol has been extensively used Migration of snails from nontreated areas into treated areas complicates this method of control The control of *S japonicum* is especially difficult because several domestic and wild mammals are natural reservoirs of the in fection Until a cheap nontoxic effective preferably oral chemotherapeutic agent is developed mass treatment cannot be at tempted with any expectation of success

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involvement ascites splenomegaly and eosinophilia should be suspected of having schistosomiasis Late in the disease there is evidence of liver cell damage and the cephalin cholesterol flocculation test thymol turbidity test and urine urobilinogen test become significantly positive The specific diagnosis is based upon finding the eggs in the feces *S mansoni* with a large lateral spine *S haematobium* with a terminal spine and *S japonicum* with a rudimentary lateral spine Eggs are not present during the incubationary period are present in numbers during the acute stage and may become few in numbers as the chronic stage progresses *S mansoni* eggs are also found in the urine in a small percentage of the infections As the infection may be light and the symptoms are not specifically diagnostic stool examination of all patients from endemic areas is indicated If the simple smear examination is negative concentration of the stool by sedimentation or the acid ether technique is required Proctoscopic examination may reveal small ulcerations or granulomatous nodules and snips of mucosa from these and even normal appearing mucosa of Houston s valve have a high diagnostic value These mucosal snips unfixed and unstained should be immersed in distilled water for five minutes pressed between two glass microscope slides and examined for eggs under the low power of the microscope Occasionally when eggs cannot be found in the feces or rectal mucosa a liver biopsy may reveal the presence of eggs Various serological and intradermal tests are useful though not widely available

Prognosis The prognosis is good in early light and moderate infections provided that specific therapy is given Chronic infections and heavy infections usually have severe extensive hepatic and intestinal damage and in these circumstances the prognosis even with therapy is relatively poor

Treatment Nutritional therapy and correction of anemia are indicated and the patient should be brought to a satisfactory physical state before being subjected to the rigors of chemotherapy Vascular shunts splenectomy and other surgical procedures may be indicated when hepatic damage is extensive The purpose of specific chemotherapy is to kill the adult worms in order to prevent the formation of toxins and the production of additional eggs Trivalent antimony compounds tartar emetic (potassium antimony tartrate) Triostam (sodium antimonyl gluconate) and stibophen (Fuadin) are the drugs of choice Stibophen though less effective than tartar emetic is less toxic and is therefore preferred by many Tartar emetic is slowly administered intravenously as a 0 5 per cent solution as follows first day 8 ml third day 12 ml fifth day 16 ml seventh day 20 ml ninth day 24 ml and on alternate days through the twenty ninth day 28 ml (total 360 ml containing 0 648 gm of antimony)

Stibophen is given intramuscularly as a 6 3 per cent solution The course of treatment for adults consists of 20 injections of 5 ml on alternate days starting with 1 5 ml and 3 5 ml on the first two injections Children are given a total dose of 1 0 ml per pound of weight in 20 injections Relapses occur not infrequently so repeated stool examinations should be made several months after the completion of therapy and a second course of treatment given if indicated Miracil D a thioxanthone which has the advantage of oral administration is ineffective against *S japonicum* and its value in *S mansoni* infection is questionable but still under investigation

VESICAL SCHISTOSOMIASIS

Schistosoma haematobium is the common cause of vesical schistosomiasis rarely *S mansoni* may be involved The adult worms inhabit the venules of the vesical and pelvic plexuses and the eggs are deposited primarily in the bladder and urinary tract

Morbid Anatomy The pathological changes depend upon the intensity and duration of the infection Inflammation of the bladder by the eggs develops with ulceration and papilloma There is an extensive hyperplasia of the bladder wall which becomes greatly thickened and inelastic The ureters become indurated and thickened and the urinary flow is obstructed with resultant pathological changes in the kidney The urethra may become inflamed and occluded and the prostate seminal vesicles and vagina heavily infiltrated with eggs The eggs in the bladder urethra and kidneys become surrounded by concretions of uric acid oxalate phosphates and eventually calcium Secondary bacterial infection contributes to the ulcerations of these various organs

Symptomatology Symptoms may not develop for years in light infections but in heavy infections symptoms may be first noticed as early as one month after infection The eggs first appear in the urine in seventy to eighty four days The most characteristic symptom is a painless hematuria usually with blood in the terminal drops of urine although the whole output may be bloodtinged As the mucosal

Life Cycles. *Taenia saginata* or beef tapeworm measures 15 to 20 feet or more in length and consists of a thousand or more proglottids The head is about pinhead in size 1 5 to 2 0 mm in diameter and has four suckers but lacks hooks The terminal gravid proglottids are about 20 mm long and 6 mm wide and contain approximately 100 000 eggs When freshly passed they are white very active and crawl about like inch worms They may creep out of the anus exuding eggs about the perianal region from the ruptured ends of the parasite s uterus Eggs are also shed in the bowel and are infectious when passed in the stool Cattle and allied animals the only known intermediate hosts ingest the eggs when grazing on land contaminated with human excreta The eggs hatch in the cow s small intestine liberating the six hooked embryos which migrate by the blood stream primarily to muscle and in three months develop into bladder worm larvae *Cysticercus bovis* In the United States and other countries where beef is eaten with only the surface seared leaving the interior raw the cysticerci may be only warmed not killed When man ingests this infected meat the head of the tapeworm enclosed in the cyst is freed attaches to the intestine grows into a complete tapeworm in two to three months and may live as long as 25 years

Taenia solium or pork tapeworm measures 6 to 10 feet in length and consists of less than a thousand proglottids The scolex is smaller than the head of a pin about 1 mm in diameter has four suckers and a circle of hooks Gravid segments either singly or in short chains are passed by man and eggs are not consistently found in the feces The eggs are indistinguishable from those of *T saginata* Hogs which feed on human feces become infected and within three months the bladder worm *Cysticercus cellulosae* develops giving rise to measly" pork Eggs ingested by man also develop into cysts Man becomes infected with the adult tapeworm by eating inadequately cooked pork This infection is uncommon in the United States but is prevalent in parts of Asia some countries of Europe and in Latin America An unsolved problem of parasitology is the frequency with which the cysticerci are found in hogs in countries where human infection with the adult worm is extremely rare

Diphyllobothrium latum the fish tapeworm is the largest tapeworm of man growing to a length of 30 feet or more with 3 000 to 4 000 proglottids The long narrow head is provided with a longitudinal groove on either side Unlike Taenia the mature proglottids discharge their eggs as they are produced A single worm produces as many as one million eggs per day These operculate eggs when discharged into fresh water develop in several weeks and a ciliated six hooked embryo (coracidium) escapes The free swimming embryos are eaten by water fleas of the genus Diaptomus or Cyclops in which they develop into a procercoid the first larval stage Fresh water fish eat the infected water fleas and a plerocercoid the second larval stage matures in the muscle of the fish This larval form when eaten in raw or insufficiently cooked fish attaches to the small intestine of man and develops into a mature worm in five to six weeks Some of the finest species of game fish constitute the sou ce of human infection This cestode is common in Europe Russia Japan parts of Africa and Canada In the United States it is present in the Great Lakes area especially in Scandinavians There are small endemic foci in Florida and California and in South America in Chile and Argentina Refrigerated fish shipped from endemic areas to urban centers in the United States serve as a source of many infections Jewish women and children who taste their gefullte fish as they season it during its preparation are not infrequently infected

Hymenolepis nana or dwarf tapeworm is the smallest tapeworm of man measuring only several centimeters in length Heavily infected patients may harbor several thousand of them Four suckers and a crown of hooks are present on the head Posterior proglottids disintegrate in the small intestine liberating eggs which are characteried by the presence of a pair of polar filaments The eggs which are passed in man s stool are infectious and require no intermediate host When swallowed the enclosed six hooked embryo invades the intestinal villi and develops into a tapeworm cyst (cercocystis) This larval tapeworm breaks out of the villus into the intestinal lumen and becomes a strobilate worm in two weeks Although *Hymenolepis nana* is able to complete its entire life cycle in a single host it also can utilize fleas and grain beetles as intermediate hosts This parasite is cosmopolitan and is the commonest cestode of man As would be expected from its mode of transmission it is more prevalent in children than in adults *Hymenolepis nana fraterna* of rats and mice will infect man but not with the same facility with which it infects its normal hosts

Hymenolepis diminuta or rat tapeworm has been reported several hundred times in man including a number of infections in the United States The actual number of infections is probably much greater Its intermediate hosts are larvae and adults of various meal moths grain beetles and fleas Man becomes infected by eating cereals harboring these infected insects

Dipylidium caninum a common tapeworm of the dog and cat has been reported occasionally as a parasite of man Fleas and lice of dogs or cats serve as intermediate hosts of this worm therefore it may be found in young children One of the writer s patients at the age of four months harbored four mature worms indicating that the infection had occurred by the age of two months Infected fleas or lice may accidentally enter the mouth of an infant or the baby may be infected by having its face licked by a dog that has just nipped a flea

Symptoms Although a patient usually harbors one or only a few *Taenia saginata* or *T solium* as many as 143 *D latum* and several thousand *H nana* have been recovered The clinical picture may be due to the number and mass of worms present the trauma produced at the sites of attachment and reaction to the metabolites of the worms Tapeworm infection frequently produces no symptoms and the patient becomes aware of his infection only when segments are passed in the stool or are found in the underclothing Tapeworms may be harbored for years and except for the inconvenience of the gravid segments crawling out of the anus the host continues in robust health enjoying both food and drink

In one study 47 of 100 patients harboring *T saginata* complained of abdominal pain described as a vague ache or hunger pain relieved by food colicky and stabbing

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SCHISTOSOME DERMATITIS

(Swimmers Itch)

Etiology Schistosome cercariae of several avian and mammalian hosts penetrate the skin of man but can progress no further and are destroyed in the skin producing a dermatitis A number of migratory birds including several species of ducks harbor the adult worms and wherever in their travels the suitable fresh water snail host is present the dermatitis may be found in man Recognition of this clinical entity is gradually expanding the known geographical distribution of the disease It was first recognized in Michigan in 1928 and now is extensively distributed in the United *States Canada Europe Mexico Central* America Japan Malaya Australia India Africa Alaska South America Cuba and New Zealand Marine forms cause a dermatitis among clam diggers and sea bathers on the east and west coasts of the United States and in Hawaii

Symptoms The skin penetration of the cercariae *is accomplished by lytic* secretions and the action of their anterior spines Within a few minutes a prickling sensation begins and persists for a half hour leaving small macules Several hours later the macules begin to develop into papules and some may become pustules Intense itching and edema accompany these lesions which reach their maximum in three days and subside in a week Scratching may lead to secondary infection Individuals vary markedly in their susceptibility The reaction to repeated infection is more severe presumably because of a local sensitization

Treatment Antipruritic and antihistaminic lotions *are of palliative value Anti*microbial drugs should be used for secondary bacterial infection

Prevention Removal of snails from bathing beaches and the destruction of aquatic growth which may harbor them is a practical method of preventing the infection A mixture of two parts copper sulfate and one part copper carbonate at the rate of three pounds per 1000 square feet of bottom is lethal to snails Cercarial penetration of the skin usually takes place as the film of water on the skin evaporates In an experimental infection brisk drying with a towel *reduced the number of cercarial le*sions on one leg to one lesion in contrast to 125 on the other leg on which the water dried slowly

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Cestode or Tapeworm Infections

(Cestodiasis)

Cestodiasis is an infection with species of tapeworms The mature worm (strobila) consists of a head (scolex) the organ of attachment which is provided with suckers and usually with anterior hooklets the neck situated immediately behind the head which constitutes the region of growth of the tapeworm and a chain of successive segments (proglottids) which arise from the distal end of the neck and become larger and more mature sexually as their distance from it increases Each mature proglottid is a complete *hemaphroditic reproductive unit* The tapeworms do not have a digestive tract but absorb food through their body wall The mature egg of human tapeworms contains an oncosphere or hexacanth embryo After the oncosphere stage there are one or more larval stages before the worm is ready to mature Most tapeworms require two or *three hosts for the completion* of their life cycles

Human tapeworm infections are of two types (1) those in which the mature worm is attached to the bowel wall—intestinal cestodiasis and (2) those in which man harbors the larval form in various organs of his body—visceral and somatic cestodiasis

INTESTINAL CESTODIASIS

Etiology Thirty or more species of tapeworms produce intestinal infection in man Only six of these are common as human parasites They are as follows *Taenia saginata* (beef tapeworm) *T solium* (pork tapeworm) *Diphyllobothrium latum* (fish tapeworm) *Hymenolepis nana* (dwarf tapeworm) *H diminuta* (rat tapeworm) and *Dipylidium caninum* (dog tapeworm)

ing 40 to 75 pounds 0 4 gm 76 to 100 *pounds 0 6 gm 100 pounds and over* 0 8 gm

Oleoresin of Aspidium An emulsion consisting of 5 0 gm or ml of oleoresin of aspidium 8 0 gm of acacia and water to make up to 60 ml is very effective One half of the dose is given early in the morning followed by the second portion one hour later The total dose for children is *4 0 ml of the emulsion per 10 pounds of* body weight

Iodoalphionic Acid (Priodax) This preparation which is used for the visualization of the gallbladder was recently reported by Shookhoff and Sterman to be effective against tapeworms They give 3 0 gm to children weighing 40 pounds or less and suggest 6 0 gm for children of 100 pounds *They consider it the drug of choice for* use in children as it is well tolerated and unlike quinacrine hydrochloride or oleoresin of aspidium does not cause vomiting

Prevention Prevention consists of (1) eating only thoroughly cooked pork (*T solium*) beef (*T saginata*) and fish (*D latum*) which contain the larval stages (2) the *sanitary* disposal of human excreta (3) protection of food against contamination by man mice and rats (*H nana* and *H diminuta*) (4) treatment of dogs and cats to free them of fleas and lice and to remove *D caninum*

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VISCERAL AND SOMATIC CESTODIASIS

The larval forms of several tapeworms give rise to echinococcosis (*E granulosus*) cysticercosis (*T solium*) cenurosis (Multiceps) and sparganosis (*D mansoni*)

ECHINOCOCCOSIS

(Hydatid Disease)

Etiology Echinococcosis is caused by the larval stage called hydatid cyst of the tapeworm *Echinococcus granulosus* The adult tapeworm is found in the dog and its relatives and the cysts commonly in sheep swine cattle camel and man *Echinococcus multilocularis* which produces an alveolar hydatid cyst in man is contracted through the tapeworm s eggs in the feces of foxes

Life Cycle The adult *E granulosus* is 3 to 9 mm in length and consists of a scolex with four suckers and a crown of hooks a neck and three segments It lives attached to the upper portion of the dog s small intestine The dog becomes infected when it is fed animal organs containing Echinococcus cysts The tapeworm eggs are passed in the dog s feces contaminating the environment Sheep and other intermediate hosts ingest the eggs while grazing children and man probably pick them up from infected soil or by fondling dogs whose fur is contaminated The ingested eggs hatch in the duodenum and the six hooked embryo penetrates the intestinal wall and is carried by the lymphatics and blood stream to the organs of the host The larva undergoes vesiculation and the resultant cyst gradually develops

Morbid Anatomy The distribution of 1802 cysts in man recorded by the Australian Hydatid Registry was liver including secondary peritoneal seeding 63 3 per cent lung 24 5 per cent muscles and fascia 4 6 per cent bone 2 6 per cent kidney 2 2 per cent spleen 1 3 per cent brain 0 9 per cent heart 0 3 per cent thyroid 0 1 per cent breast 0 1 per cent and parotid prostate and pancreas 0 1 per cent The cysts are usually more or less spherical and consist of (*a*) an outer non nucleated *hyaline laminated layer* (*b*) *an inner* germinal layer (*c*) straw-colored fluid filling the cyst (*d*) daughter cysts and (*e*) brood capsules containing scolices (hydatid sand) The germinal layer secretes the laminated membrane and brood capsules arise by proliferation of its nucleated cells Scolices are formed within the brood capsule from buds of its inner surface Innumerable brood capsules may be formed and on rupturing their scolices escape into the mother cyst where they are known as hydatid sand Endogenous daughter cysts probably arise from the germinal membrane brood capsules or scolices Exogenous daughter cysts arise from herniations of the wall of the mother cyst

Geographical Distribution Echinococcus has a cosmopolitan distribution with areas of heavy infection in sheep raising countries where diseased organs are discarded to the dogs Especially heavy infection rates among dogs domestic animals and man are found in South Africa Australia New Zealand the Punjab (India) Mediterranean countries sheep raising areas of South America and among the Eskimos of Canada and Alaska In Canada the moose wolf dog cycle provides man with the infection This parasite is not uncommon in man in the United States but except for 40 autochthonous cases the infection is found in immigrants from Eastern Europe or was acquired in other foreign endemic areas The size of the cysts makes their detection at meat inspection almost certain and condemned organs are rendered noninf ctious when they are cooked for tankage Echinococcosis is uncommon in dogs in the United States The prevalence of such soil borne human helminths as Ascaris and Trichuris in the southern United States indicates that favorable conditions for the spread of the eggs of Echinococcus are present

Symptoms The symptoms of echinococcosis are those of a slowly growing tumor

Pain was frequently associated with digestive disturbances such as distention vague discomfort a gnawing sensation hungry feeling flatulence and nausea One third of the patients complained of giddiness especially when hungry but only 7 per cent experienced an increase in appetite Weight loss occurred in some patients but most of the group maintained their weight and some even gained weight Constipation and diarrhea were not significant A mild anemia was present in less than 10 per cent of the patients eosinophilia of 6 to 13 per cent in 10 per cent of the patients and a relative lymphocytosis in 30 per cent of the group

Diphyllobothrium latum perhaps because of its great size and the presence of multiple worms apparently is responsible for more symptoms than the other tapeworms Anemia due to this infection is present in less than 1 per cent of the patients afflicted Few of the infections originating in the United States have had an accompanying history of tapeworm anemia The anemia is hyperchromic with erythrocyte counts as low as 500 000 per cu ml and a color index of 1 07 A leukopenia and varying degrees of eosinophilia may be present The gastric acidity is usually normal Complete remission of the anemia follows expulsion of the tapeworm There is a rapid regeneration of erythrocytes and a marked reticulocytosis begins within a week if the extrinsic factor is present Van Bonsdorff's studies suggest that because of the parasite s effect on the reaction of intrinsic and extrinsic factors anemia is more common in patients whose tapeworm is attached high up in the intestine It is postulated that the tapeworm absorbs the intrinsic factor *D latum* actively absorbs 10 to 50 times as much vitamin B_{12} as do other tapeworms

Light infections with *H nana* usually produce no symptoms other than vague abdominal distress due to a mild enteritis Children harboring hundreds of these worms may experience abdominal pain diarrhea headache and minor nervous disturbances Slight anemia and eosinophilia may be present

Diagnosis The diagnosis of the large tapeworms is commonly made by the patient s recognizing characteristic proglottids in his feces or underclothes Segments of *T saginata* and *T solium* have lateral genital pores and these two species can be differentiated by the number of lateral uterine branches The proglottids of *D latum* are broader than long the dark egg filled uterus is rosette shaped and the uterine pore is in the middle of the segment Proglottids or artifacts which are digested beyond recognition should be teased apart and searched under the microscope for eggs which remain intact although the segment has disintegrated The eggs of all of the tapeworms will also be found in the stool those of *H nana H diminuta* and *D latum* with greatest regularity The large tapeworms are sometimes detected by roentgenography following a barium meal

Treatment Quinacrine hydrochloride (Atabrine) is the drug of choice against tapeworms Oleoresin of aspidium is equally effective but is potentially more toxic Both of these drugs lose some of their effectiveness in children because of the frequent occurrence of vomiting following their administration Either adults or children who vomit these drugs may be successfully treated by duodenal tube Recently iodoalphionic acid (Priodax) has been demonstrated to be of value against tapeworm in children Preparation of the patient is necessary before an anthelmintic is administered On the day preceding treatment the patient should be placed on a liquid diet and supper should be omitted except for black coffee tea or water A soapsuds enema should be given in the evening A saline purgative should be given to patients under treatment for *Hymenolepis nana* the evening preceding treatment The patient should remain in bed and the following morning breakfast is omitted and the anthelmintic administered Two hours after the administration of the last dose of anthelmintic a saline purge is given to flush out the injured or dead worm If the worm is not brought out by purgation or if the head is not recovered a soapsuds enema should be given since the worm or scolex may be lodged in the large intestine Toilet paper used by the patient should not be placed in the bedpan as it makes the search for the tapeworm head very difficult The large tapeworms are frequently removed by a single course of therapy *H nana* infections are much more difficult to cure because of the large number of worms usually present

Quinacrine Hydrochloride (Atabrine) The adult dose of quinacrine hydrochloride is 0 8 gm To prevent vomiting the total dose may be divided in two portions and given at a half hour interval Children are given the following total dose those weigh

available Chemotherapy is entirely ineffective It is possible that roentgen irradiation may be of value Biotherapy consisting of the injection of increasing amounts of hydatid fluid in an attempt to desensitize the tissues and and kill the parasite has been tried in patients with multiple or inoperable cysts

The location size and condition of the cyst determine the surgical course to be pursued As more than one cyst is present in 25 to 50 per cent of the patients exploration is necessary Alveolar osseous and multiple cysts are often not amenable to surgery Extensive spread of the cysts in the pleural and peritoneal cavities may require multiple operations over a period of years to allay pressure If the cyst is unilocular and there is danger of its rupture during removal the cystic fluid may be replaced by 2 per cent formalin and allowed to act for five minutes or sufficient commercial formalin should be injected to give the cystic fluid a 2 per cent concentration to kill the germinative portions Whenever possible the cyst should be enucleated but a calcified cyst of the liver might be kept under observation without surgery Marsupialization may be necessary especially when the cyst is infected The skin test remains positive for years after removal of the cyst but the complement fixation test soon becomes negative

Prevention In endemic areas avoidance of contact with dogs or their contaminated environment is important in the prevention of hydatid cyst Children especially should be protected and taught the value of hand washing Periodic deworming of dogs with arecoline hydrobromide is necessary to keep them free of Echinococcus Carcasses of sheep hogs and cattle should be inspected at slaughter and organs infected with cysts destroyed Dead animals should be buried to prevent dogs from feeding upon them

CYSTICERCOSIS

Etiology Cysticercosis is infection with the cyst stage of Taenia The cyst usually involved is *Cysticercus cellulosae* of the pork tapeworm *T solium* Cysticercosis of man due to *T saginata* the beef tapeworm has been reported only occasionally

Life Cycle Man may acquire the cyst by the ingestion of *T solium* eggs from contaminated soil or food As the egg is infectious when passed in the stool patients harboring the adult worm may become infected through anus to mouth contamination Auto infection may occur through regurgitation of the eggs or segments into the stomach by reverse peristalsis The eggs hatch in the upper intestine and the embryos migrate by way of the lymphatics and blood stream to various organs of the body They develop into translucent bladder worms 5 by 10 mm in two to three months

Symptoms The invaded organs in order of frequency are the subcutaneous tissues muscles brain eye heart lung and peritoneum The presence of hundreds of cysticerci in the subcutaneous tissues and muscles may go unnoticed or may cause only slight muscular discomfort As many as 20 000 cysticerci have been found in one patient In the brain the cysticerci vary in number size and location If single or few in number they may cause no symptoms As long as the cysticerci remain alive minimal inflammatory reaction develops The dead parasite causes local inflammatory tissue reaction and capsule formation Epileptic seizures and other disturbances due to tumor may be present Ventricular cysticerci may produce blockage of cerebrospinal fluid There may be an increase in cerebrospinal fluid glucose total cell count and eosinophils In countries where *T solium* is prevalent as high as 10 per cent of the brain tumors are cysticerci Surgical removal is the only treatment available but this may not be practical if the cysticerci are numerous Invasion of the eye by *Cysticercus cellulosae* may lead to uveitis iritis detachment of the retina and hemorrhage The parasite is unencapsulated and constantly changes shape

Diagnosis The diagnosis of cysticercosis except in endemic centers is difficult and usually awaits excision of the larva The presence of an adult *T solium* in as many as 25 per cent of the patients with cerebral or ocular cysticercosis is of considerable diagnostic significance Likewise the presence of subcutaneous cysticercosis is often accompanied by a similar infection of the brain The onset of epileptic seizures after childhood in endemic areas suggests cysticercosis Biopsy of subcutaneous cysticerci gives a specific diagnosis Calcified cysticerci are visible on roentgenographic examination Eosinophilia is inconstant as are intradermal and complement fixation reactions

CENUROSIS

A cenurus is the larval stage of tapeworms belonging to the genus Multiceps the adults of which live in the intestines of dogs and cats Sheep and rabbits are the usual hosts of the cenurus it has been reported in man 10 times *Coenurus cerebralis* infection which localizes in the brain is usually

and depend upon the organ involved A cyst may attain considerable size and may extensively involve an organ without causing symptoms The rate of growth is extremely variable and depends upon restriction of the invaded tissue Nutrition also is apparently important for in vascular organs like the spleen and lungs the growth of the cyst is rapid The average growth is 1 to 2 cm in diameter per year

As all of the hexacanth embryos entering the portal stream pass to the liver this organ is the most common site of hydatid cysts The right lobe of the liver harbors the majority of the cysts which are often single The liver is extraordinarily tolerant to the presence of this parasite and calcified cysts 8 to 10 cm in diameter often produce no symptoms despite years of residence in this organ Liver function is usually not significantly altered but transient jaundice due to pressure on the biliary tract may be present Ascites and enlargement of the abdominothoracic veins may follow cystic pressure in the area of the portal fissure Large cysts may produce a sense of weight accompanied by nausea and distention after meals Rupture of hepatic cysts may cause extension into the liver or into the lungs and frequently results in an extensive invasion of the lowest portion of the peritoneal cavity The multitude of liberated brood capsules daughter cysts and scolices grow apace Pressure on the colon urinary bladder and ureters is often the patient s first presenting symptom

Pulmonary echinococcosis occurs twice as frequently in the right lung as in the left The cysts are surrounded by adventitial capsules of considerable thickness Cough is a common symptom Pain is rarely severe and usually takes the form of discomfort or a feeling of a weight in the chest Hemoptysis is frequently present and may be induced by coughing Rupture of pulmonary cysts may cause pneumonia anaphylactic shock extensive pleural invasion or simply evacuation of the cyst contents through the bronchus

Hydatid cysts of the brain fortunately are rare They are more common in children than in adults and because of the slow growth of the parasite may have a considerable period of latency The usual signs and symptoms of an expanding tumor are present Jacksonian epileptiform seizures followed by paralysis are often present Cardiac cysts may be silent may perforate into the pericardium or may produce dissemination throughout the blood stream Kidney cysts may cause pain hematuria and altered kidney function

Secondary bacterial infection of cysts occurs especially of those in the liver The latter may be diagnosed as cholecystitis The suppurative process may extend into the peritoneal cavity and give rise to a subphrenic abscess or general peritonitis

Puncture or rupture of hydatid cysts may produce toxic manifestations in sensitized persons These anaphylactic reactions may consist of only urticarial wheals with general or localized erythema and pruritus Other symptoms of variable occurrence are fever cyanosis dyspnea abdominal pain vomiting diarrhea and syncope As the anaphylactic state is abolished by general anesthesia grave symptoms rarely if ever occur during operation even if much hydatid fluid is spilled into the operative area

Diagnosis The clinical diagnosis of hydatid cyst is based upon the presence of a cystic tumor often in a patient enjoying good health Hydatid thrill is extremely rare and the cysts are often too tense to show fluctuation Roentgenographic examinations are especially valuable in diagnosis and unsuspected cysts are often located The cysts are identified by their spherical shape fluid content calcified wall and adventitial thickening Laboratory diagnosis of pulmonary cysts may be made by finding scolices brood capsules or cyst fragments in the sputum or in the urine in kidney cysts Exploratory puncture for diagnostic purposes is dangerous as it may result in an anaphylactic reaction or dissemination of the infection Eosinophilia is very irregular in hydatid disease and is unreliable for diagnosis The intracutaneous test (Casoni) using hydatid fluid gives 75 to 95 per cent positive reactions Consequently a negative reaction is of relative value in excluding the presence of infection Reactions are most frequently positive when the cyst is in the liver and lungs but are often negative with cysts of the brain and bones A positive complement fixation test is also of value and suggests that the infection is still active A hemagglutination test is being developed

Prognosis In general the prognosis of echinococcus cyst is good but depends upon the site of the cyst and the possibility of its rupture and spread Alveolar cysts because of their extensive spread and invasiveness are most dangerous Repair of bones invaded by cysts is usually unsatisfactory

Treatment Surgical removal of the hydatid cyst is the only successful therapy

variety of carnivorous and herbivorous animals The chief reservoir for human infection is swine The incidence of infestation in hogs fed on grain or allowed to root in the field is about 0 5 per cent but in those fed on uncooked garbage it is in the range of 5 per cent The meat becomes infectious within seventeen days after the pig ingests the parasite

The epidemics which occur are small and are usually confined to a family or group which has held a picnic or barbecue Infection may follow the tasting of raw pork as in the preparation of sausage In meat products prepared commercially from the pooled muscles of many hogs the infected sample is so diluted that the infestation in any given person is light though it may be spread among many people Only about 70 per cent of the pork raised in this country is processed in plants which are under close supervision hence a large part of the country s total supply of pork products may carry live parasites As much as 10 per cent of the sausage in large city markets has been found infected It has been estimated that each American consumes three servings of trichinous pork in a year The cysts do not calcify in pork and are almost invisible to the naked eye hence they are not looked for in the government inspection of meat No economically feasible technique for detecting trichinella infection in hogs by anatomical or immunological methods has been developed

Autopsy studies indicate that approximately 16 per cent of the human population is infected this incidence is the same in both sexes The fact that the number and density of infections are greater in older patients suggests many separate invasions of the body by a small number of parasites The greater prevalence of the disease in the Midwest and other areas where Germans and Italians have settled reflects local customs in the preparation of food

Pathogenesis and Morbid Anatomy Invasion of the intestine by the adult parasite produces little local reaction About the seventh day the larvae enter the general circulation and are widely distributed to all tissues they then break out of capillaries between muscle fibers and penetrate into serous cavities and even into the cerebrospinal fluid In initial infections invasion of striated muscle fibers produces necrosis hyaline degeneration and an inflammatory response consisting of polymorphonuclear neutrophils lymphocytes and variable numbers of eosinophils The reaction of the body produces around the coiled trichina a cyst which begins to calcify between six and eighteen months after invasion and in which the larvae may live for ten years or more

The heaviest infestation occurs near the tendinous portion of the diaphragm of the gluteus pectoral deltoid gastrocnemius or intercostal muscles in that order of frequency The extraocular muscles the masseters and the muscles of the larynx may also be involved The heart is invaded but the parasite seems unable to establish itself in cardiac or smooth muscle

In approximately four fifths of the human infections proved at autopsy less than ten trichinae per gm of muscle are present— a degree of infection which probably produces few symptoms In some cases however as many as 1000 trichinae per gm of muscle may be found

In reinfections the muscle walls of arterioles may show degenerative and inflammatory changes similar to those seen in serum sickness and periarteritis nodosa—a finding which suggests an allergic or immune reaction The fatty change found in the liver in fatal cases probably results from inadequate intake of protective foods The renal tubules occasionally show degenerative changes which are reflected clinically by albuminuria The bone marrow shows hyperplasia chiefly in eosinophilic myelocytes

Pathological Physiology and Chemistry The mechanism responsible for the development of edema is obscure The number of capillaries mechanically ruptured is inadequate to explain it and production of a toxin by the parasite or by the destruction of muscle has never been demonstrated Measurements of the fluid space in animals indicate that the increased permeability of capillary walls and of cells may result from an immune reaction

In some instances the blood chlorides and total serum proteins (particularly the albumin fraction) are decreased and the nonprotein nitrogen is elevated

In cases with neurological involvement the cerebrospinal fluid may contain erythrocytes and increased amounts of protein

Symptoms The symptoms are highly variable and depend largely upon the degree of infection If the meat is heavily infected the *invasion* of the intestinal mucosa one to four days after ingestion may cause local irritation producing symptoms of nausea vomiting and diarrhea which resemble those of food poisoning In other

fatal It has been reported once from the United States in a 26 month-old child from Nevada At autopsy a cenurus 3 cm in diameter was found in the frontal section of the brain and numerous budding vesicles covered the ventral aspect of the pons and medulla oblongata

SPARGANOSIS

Sparganosis is due to infection with the second larval stage of the tapeworm *Diphyllobothrium mansoni* of the dog This larva called a sparganum or plerocercoid may be acquired by ingesting water containing water fleas (Cyclops) harboring the first larval stage (procercoid) by eating raw infected (plerocercoid) flesh of snakes frogs birds and mammals or by applying their parasitized tissues to an inflamed or ulcerated site Infections of the eye are produced by the latter method The sparganum may grow as long as 30 cm and may cause considerable inflammatory reaction especially in the abdominal wall and orbital region Surgical removal of the sparganum is the only treatment available The disease is found primarily in the Far East but is also present in Africa Europe Australia North and South America

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The Nemathelminthes (Roundworms)

Nematoda or roundworms infecting man vary greatly in size are unsegmented and are cylindrical in shape They are completely covered by a cuticular acellular layer There is a complete digestive tract and the sex organs are greatly elaborated occupying the major part of the body cavity Most nematodes are oviparous but a few are larviparous Eggs of some species are fully embryonated and infectious when laid others require a period of incubation within or outside the human body Eggs of some nematodes hatch in the soil grow and metamorphose into infective stage larvae Several nematodes require an intermediate host for completion of their larval development Man acquires most nematode infections by the ingestion of infectious eggs but hookworm and strongyloides larvae actively invade the skin filaria larvae gain entrance into the skin after escape from their blood sucking insect hosts and Trichinella infections are acquired from infected pork

The following important nematode infections of man will be considered here trichinosis trichuriasis strongyloidiasis ascariasis visceral larva migrans enterobiasis filariasis dracunculosis hookworm and creeping eruption

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Trichinosis

(*Trichiniasis Trichinelliasis*)

Definition Trichinosis is an infestation of striated muscle by the larvae of the roundworm *Trichinella spiralis* It is transmitted by inadequately cooked food and is one of the greatest uncontrolled public health problems in this country

Etiology Live encysted larvae of the parasite are ingested in meat After being liberated by protein digestion they anchor themselves to the mucosa of the duodenum and jejunum from which they extract oxygen and liquid food Within the next two days they develop into sexually mature adults—the males 1 5 mm and the females 3 to 4 mm in length After copulation the male may die but the female burrows *deeper into the mucosa The eggs* develop and hatch *in utero* About 1500 larvae (which are 100 μ in length) are discharged through the vulva in the anterior fifth of the body into the lymphatics and lacteals of the host s small intestine at the rate of one each half hour over a period of approximately six weeks the female then dies

Epidemiology The parasite exhibits no specificity for species and can infect a wide

count is usually between 10 000 and 20 000 per cu mm The eosinophilia precedes the development of positive skin or serological reactions but may be absent in severe infections or suppressed by a simultaneous bacterial infection In subclinical or very mild cases the eosinophil count is of no diagnostic value Eosinophilia may persist for five to seven years

Reversible changes in the T waves may be detected by electrocardiograms after the second week of the disease

Prognosis In subclinical or mild infections the prognosis is excellent in small epidemics the mortality may vary from 5 to 30 per cent The over all mortality must be low since few patients in whom the infestation is detected at autopsy have had clinical symptoms suggestive of the disease In individual cases the ultimate prognosis is poor if symptoms particularly pronounced diarrhea develop within two days of exposure or if little evidence of immune response can be detected by eosinophil counts skin tests or serological reactions Most patients who die succumb to pneumonia or cachexia between the fourth and sixth weeks

Treatment No specific treatment is known If the parasite can be demonstrated in the suspected meat while the patient is still having gastrointestinal symptoms administration of an anthelmintic such as piperazine citrate (which is also effective in related parasitic infestations) in doses of 1 0 to 1 5 gm twice daily for seven days may remove some of the adult worms

No drug has been found effective against the larvae After encystment of the parasite has begun the damage is done

In human cases and in experimental animals the administration of corticotropin (ACTH) or adrenal corticosteroids has reduced the acute manifestations of the disease The benefit probably results from suppression of host response to the presence of the parasite or its products The dose and duration of hormone therapy must be carefully adjusted to the individual case

Because of the tendency to hypoproteinemia a high protein diet is probably of some value in supportive therapy In very heavy infections with severe symptoms and marked edema caution should be exercised in the administration of crystalloids such as glucose and saline Infusions may be necessary to overcome dehydration but unless the intravascular osmotic pressure is maintained with plasma or human serum albumin circulatory collapse may be produced by fluid replacement therapy

The muscular aching may require the intermittent administration of analgesics such as salicylates It is possible that the administration of antihistamine drugs from the second to the fifth week might reduce the allergic manifestations of the disease

Prevention All the basic scientific facts necessary for complete prevention of trichinosis in human beings have been known for years Trichinae can be killed by cooking or irradiation Smoking pickling and other methods of processing or preserving meat do not kill the parasite Pork should be cooked at a minimum temperature of 140° F for at least thirty minutes per pound otherwise large roasts may not be completely done in the center Freezing of meat at 0 F (—18 C) for at least 24 hours or at 5 F (—15 C) for twenty days will usually kill all trichinae These preventive measures are effective and their general use has been shown by autopsy studies to reduce the incidence of human infection

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Trichuriasis

(Whipworm Infection Trichocephaliasis)

Etiology The adult *Trichuris trichiura* measures 30 to 50 mm in length the female is usually longer than the male These parasites have a characteristic whip like shape the handle of the whip comprising the posterior two fifths and the delicate narrow esophagus the anterior three fifths They live primarily in the cecum and colon of man

Life Cycle The female worm passes several thousand barrel shaped eggs daily which bile stain to a beautiful golden brown Embryonation of the egg takes place in three to four weeks in warm moist soil Man becomes infected by ingesting the fully embryonated egg the shell of which is weakened in the upper intestine where the larva is freed The young worm temporarily attaches to the small intestine later passing to the site of its adult attachment in the cecum where it grows into an adult

cases these symptoms may be entirely ab sent

Beginning on the seventh day the *migration* of the larvae usually produces muscular weakness stiffness or pain accompanied by remittent fever which may reach 104° F (40° C)—a rare finding in disease caused by larger parasites The fever may persist for several weeks and usually drops by lysis The elevation of temperature as well as occasional transient skin rashes probably results from the liberation of foreign protein since a large number of larvae are destroyed during their migration Depending upon the muscles invaded the patient may note backache which resembles that of influenza or pain on chewing swallowing breathing or moving the eyes or limbs

Next to the muscular symptoms edema is the most common finding it may appear at any time after invasion Edema is most frequently manifested as puffiness around the eyes involving the upper lids though it may be generalized Many of the protean manifestations of the disease result from the involvement of arterioles and from the edema Symptoms in the central nervous system such as headache delirium and psychic or visual disturbances suggest encephalitis but are usually transient Hemiplegia or localized paralysis occasionally occurs and may be permanent Dyspnea may result from the edema and from invasion of the muscles of respiration The great variety of symptoms the variation in their intensity and the lack of regularity in the course are characteristic of trichinosis

After *encystment* the only symptom may be vague aching in the muscles

Diagnosis A *clinical* diagnosis is extremely difficult to make except in cases of heavy infection The early gastroenteritis is nonspecific The most useful physical signs are tenderness to pressure on the muscles edema especially about the eyes the splinter hemorrhages under the nails or in the conjunctivae Only a fraction of the cases are recognized and reported

Laboratory methods are helpful for confirmation of the diagnosis but are of little aid in therapy If a portion of the suspected meat can be obtained it should be ground in a household meat chopper and digested in hydrochloric acid and pepsin After the suspension has been digested for an hour several portions are examined for larvae by means of a dissecting microscope

Examination of the stools for adult worms is useless During the stage of migration larvae can occasionally be found in the centrifuged blood

Beginning ten days after infection the larvae may be found in biopsy specimens removed from the tendinous insertion of the deltoid or gastrocnemius muscle One gram of the unfixed muscle should be spread between two pieces of plate glass measuring roughly 18 by 12 by 0 6 cm compressed with screw clamps and examined under the low power microscope During the second or third week the larvae may be parallel to muscle fibers and are sometimes difficult to recognize After encystment they can hardly be confused with anything else The samples removed at biopsy are usually too small to examine by the digestion technique Routine methods of cutting and staining microscopic preparations rarely detect the parasite and show only a myositis

The simplest diagnostic procedure is the intradermal skin test performed by injecting 0 1 ml of a 1 10 000 dilution of dried powdered trichinae dissolved in saline A positive reaction is usually not obtained before the end of the third week of the infection The skin reaction may be immediate (wheal) or delayed (tuberculin) in type Many false positive tests are obtained some are group cross reactions due to infestations with closely related parasites (such as Trichuris the whipworm) but the significance of most is unknown The skin test usually remains positive for about seven years

Immunological tests made on the patient s serum after the third week of the disease and utilizing the precipitin complement fixation or flocculation techniques are more specific but may not be positive in an overwhelming infection Involvement of the reticuloendothelial system particularly with Hodgkin s disease may give rise to false positive reactions The most accurate serological reaction uses living trichinella larvae suspended in the patient s serum a highly refractive precipitate forms around the worm This mechanism probably explains how most of the ingested living larvae are prevented from penetrating the intestinal mucosa in reinfections The serological tests revert to negative after a year

In acute infections caused by a moderate number of parasites the eosinophils in the peripheral blood will begin to increase ten days after infection reaching a peak in the third or fourth week The proportion of eosinophils may vary from 5 to 70 per cent and the total leukocyte

Strongyloidiasis

(*Strongyloidosis*)

Etiology Strongyloidiasis is a chronic intestinal infection caused by a delicate nematode *Strongyloides stercoralis* The disease is due to the presence of adult worms in the gastrointestinal mucosa and to the migration of larvae through the intestinal mucosa and other organs

Life Cycle The parasitic female is 2 2 mm in length and lives partially buried in the mucosa of the duodenum and jejunum but in heavy infections may be found from the pylorus of the stomach to the rectum A parasitic male worm has been described which is practically indistinguishable from the free living male The writer collected several thousand parasitic females at an autopsy but was unable to find a single parasitic male Single larval infections of the rat strongyloides always produce fertile parasitic female worms indicating that parthenogenesis occurs The parasitic female worm lays thin shelled eggs which embryonate within the glands stroma and epithelium of the mucosa The escaping rhabditiform larvae burrow out to the intestinal lumen and initiate three types of life cycle (1) In the direct cycle the rhabditiform larvae pass out in the feces and develop in the soil into infectious filariform larvae which penetrate man s skin (2) In the indirect cycle the rhabditiform larvae pass out in the feces and in the soil develop into free living male and female worms The female lays eggs that hatch into rhabditiform larvae which develop into infectious filariform larvae (3) In the hyperinfective cycle the rhabditiform larvae develop into the filariform stage in the intestine and by penetrating the intestinal mucosa or perianal skin establish a cycle within the host without leaving the body (autoinfection) Internal hyperinfection explains strongyloidiasis in persons who have been out of endemic areas for as long as thirty six years Filariform larvae in the soil penetrate human skin on contact and enter the venous blood stream They are carried to the right heart and lungs They penetrate the pulmonary capillaries into the alveoli and migrate up the respiratory tree to the pharynx and are swallowed The worms grow considerably during this migration and the young forms when they arrive in the duodenum burrow into its wall and within twenty eight days from skin exposure begin to lay eggs

Geographical Distribution Strongyloidiasis is cosmopolitan and parallels the distribution of hookworm but usually is somewhat less prevalent It occurs in the rural southern United States and has been found as far north as New York State Dogs and cats may harbor Strongyloides but they are not favorable hosts man is the important reservoir

Pathology The invasion of the skin by the filariform larvae may cause erythematous papular eruptions Napier described a periodic petechial urticarial or linear eruption with bathing trunk distribution The adult females eggs and larvae are found in the intestinal mucosa and by toxic and lytic action produce an eosinophilic inflammatory reaction in the lamina propria Larvae may migrate through the muscularis and serosa into the peritoneal cavity Migration of larvae through the lungs especially in large numbers as encountered in the hyperinfective cycle produce localized inflammatory reaction and hemorrhage The cellular response consists of polymorphonuclear neutrophils eosinophils mononuclears and endothelial cells The bronchial epithelium is involved and congestion of the bronchioles may trap the migrating larvae which metamorphose into adults Larvae are found throughout the lung in the pulmonary arterioles alveoli subpleural and intrapulmonary lymphatics Larvae have been found in large numbers in the liver and in practically every organ of the body usually surrounded by eosinophilic granulomata

Symptoms Although larval penetration of the skin causes some inflammation and itching the history of "ground itch" often cannot be elicited (see Hookworm Disease p 407) As Strongyloides and hookworm are frequently present in the same patient it is impossible to identify the cause of the ground itch if it is present Light infections frequently cause no intestinal symptoms In moderate infections abdominal pain is the most common symptom and it is often associated with periodic watery diarrhea alternating with constipation or normal bowel movement Severe infections usually due to autoinfection cause anemia appetite loss nausea vomiting emaciation and dysentery Fever cough and a tender liver indicate massive larval migration During the early and acute phases of the infection a leukocytosis of 8000 to 20 000 per cu mm with a 10 to 50 per cent eosinophilia is characteristic In chronic infections the leukocyte count may be within normal limits with 2 per cent to 10 per cent eosinophils Overwhelming infections with fatal termination have been associated with (1) paralytic ileus (2) hepatitis cholecystitis and myocarditis (3) *E coli* bacteremia and meningitis probably spread by the massive larval migration from the intestine to the blood stream Genitourinary complications with a history of nocturia incontinence urgency genital urticaria and larvae in the urine have been reported

Diagnosis Clinical diagnosis is uncertain as hookworm Trichuris and *E histolytica* infections may produce somewhat similar clinical pictures The presence of rhabditiform larvae in a fresh stool is diag

worm in several months The adult worm lives for many years

Epidemiology *Trichuris trichiura* is a cosmopolitan parasite of the warm moist regions of the world *It is frequently one* of a trinity of infections (hookworm Ascaris and Trichuris) Stoll calculated the world prevalence of Trichuris infection to be 355 million In the United States Trichuris has a spotty distribution and occurs abundantly only in areas where there is dooryard pollution dense shade close to the house and a heavy rainfall These conditions are especially prevalent in the southern Appalachians and southwestern Louisiana As many areas in Puerto Rico meet these environmental conditions heavy infections are frequently encountered in emigrants from that Commonwealth In general children are more frequently and more heavily infected than adults

Pathology and Symptomatology Trichuris lives primarily in the cecum of man but is also found in the appendix and lower ileum In heavily parasitized persons the worms are distributed throughout the colon and rectum and they may be seen on the prolapsed rectal mucosa that results from straining at the frequent stools The worm embeds its long threadlike anterior end into the intestinal mucosa

Light infections usually do not give rise to recognizable clinical manifestations and the presence of the parasite is discovered only on routine stool examination In a group of 81 patients with uncomplicated heavy Trichuris infection Swartzwelder noted that abdominal or epigastric pain was the most frequent complaint and that it was often accompanied by localized areas of tenderness Nausea and vomiting constipation distention and flatulence slight fever and headache also occurred relatively frequently Approximately one half of the patients had a tentative diagnosis of some form of appendicitis the chronic form predominating Patients with very heavy chronic Trichuris infections present a characteristic clinical picture consisting of severe anemia frequent small blood streaked diarrheic stools abdominal pain and tenderness weight loss and occasional rectal prolapse with worms embedded in the mucosa Extreme cachexia is sometimes seen and fatal termination in children harboring from 400 to 4100 worms has been reported Trichuris may attach to the appendiceal mucosa and may provide an entrance for pyogenic bacteria and subsequent acute or subacute inflammatory processes

The anemia that accompanies Trichuris infections may be marked with a hemoglobin value as low as 3 0 gm *The worms* apparently suck the blood of their host and hemorrhage may occur at the site of their attachment Not infrequently the Trichuris infection is accompanied by other helminth and protozoan infections making it impossible to determine the exact role of Trichuris in the anemia An eosinophilia is encountered in uncomplicated Trichuris infections especially recently acquired infections Chronic infections may be accompanied by a moderately elevated or normal eosinophile count

Diagnosis As light infections are usually asymptomatic and heavy infections may be confused with hookworm disease amebiasis or appendicitis stool examinations are necessary for a definitive diagnosis The simple smear technique will detect most of the infections but it may be necessary to employ a concentration technique in light infections An egg count using Stoll s method will give an approximation of the intensity of infection and is useful in assessing the results of treatment

Treatment The treatment of Trichuris infections by means of anthelmintics administered orally until recently has been only moderately satisfactory Tetrachlorethylene hexylresorcinol and oil of chenopodium remove some of these parasites but repeated treatment frequently fails to eliminate the infection completely This failure is probably due to the worm s position in the ileocecal region which prevents the orally administered anthelmintic from reaching the parasite in lethal concentration

Recently Dithiazanine 3-ethyl 2 [5 (3 ethyl 2 benzothiazolinylidene) 1 3 pentadienyl] benzothiazolium iodide given orally has been shown to be very effective complete cures being achieved with 200 mg three times a day for three to five days

Prevention As trichuriasis is associated with soil pollution and personal cleanliness prophylaxis depends upon sanitary disposal of feces and education in hygiene

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infiltration asthmatic attacks and edema of the lips Some instances of Loeffler s syndrome and tropical eosinophilia have been attributed to migrating Ascaris larvae In stances of endophthalmitis have been observed for which the eye was removed and the sections revealed nematode larvae which were probably Ascaris Koino ingested 2000 embryonated Ascaris eggs of human source at one time and thereby demonstrated that large numbers of larvae simultaneously migrating through the lungs may cause a serious hemorrhagic pneumonia Keller Hillstrom and Gass noted widening in the hilar regions and increased bronchovascular marking in the chest roentgenograms of a group of Tennessee children infected with Ascaris Fiske in Nigeria attributes the high bronchopneumonia rate in children of over five months of age to the migration of Ascaris larvae Encephalitis and meningitis have been reported in Ascaris infected patients suggesting that the migrating larvae may reach the brain more commonly than is realized

Serious and sometimes fatal effects of ascariasis are due to the migrations of the adult worms They may be regurgitated and vomited escape through the external nares or rarely be inhaled into a bronchus Many instances of invasion of the bile ducts gallbladder liver and appendix have been reported The worms may carry intestinal bacteria to these sites and stimulate the production of abscesses The worms may penetrate the intestinal wall migrate into the peritoneal cavity and produce peritonitis Continuing their migration they may come out through the body wall usually at the umbilicus in children and the inguinal region in adults Intestinal volvulus intussusception and obstruction may also result from Ascaris infection Carbon tetrachloride as used for hookworm treatment and fever are two of the causative factors of Ascaris migration

Even when the worms cause little or no traumatic damage the by products of living or dead worms may produce marked toxic manifestations in sensitized persons such as edema of the face and giant urticaria accompanied by insomnia loss of appetite and weight extreme nervousness and in extreme cases cachexia Some workers believe that they can demonstrate physical and mental retardation in infected children but factors such as heredity malnutrition and other parasites confuse the clinical picture Young pigs infected with Ascaris do not gain weight normally and it is possible that the human Ascaris may affect children similarly This action may be due to the food actually consumed by the worms or to the trypsin inhibiting substance which they produce interfering with the host s protein digestion

Diagnosis The large number of eggs passed by the female worms assures the diagnosis by the microscopic examination of simple smears of the patient s stool Fertilized eggs are very characteristic with their bile stained mammillated outer shell but unfertilized eggs assume bizarre shapes and may be mistaken for debris by the untutored or unsuspecting Rarely one encounters infections consisting of only immature worms only male worms or worn out female worms and hence eggs are not present in the stool These infections are sometimes incidentally discovered by roentgenographic examination after a barium meal Either the worm displaces the barium or the barium is retained in the worm s ribbon like intestinal tract after the host has evacuated the barium A first-class department of radiology will detect such infections from time to time when the laboratory has reported the stool negative for eggs The spontaneous passage of one or more worms by anus or mouth does not necessarily mean that additional worms are present This can be verified by stool examination two or three days after the worms have been evacuated

Treatment Piperazine salts are safe and very effective in ascariasis a single dose will cure 75 to 85 per cent of the infections A dose on two consecutive days will eliminate approximately 95 per cent of the infections Piperazine can be given at any time of day since the presence of food in the digestive tract has little if any effect on its activity against Ascaris Purgation is not required The ascarides are usually passed relaxed though still alive by the patient on the first second or third day after treatment Piperazine citrate syrup has been used successfully in partial intestinal obstruction due to ascariasis combined with abdominal decompression with a Levin tube and supportive therapy

Dosage Schedule for One and Two Day Treatment of Ascariasis with Piperazine Citrate

PATIENT S WEIGHT (lbs)	DAILY DOSE OF CITRATE SYRUP (ml)	DAILY DOSE AS HEXAHYDRATE (gm)
30–50	20	2 0
51–100	30	3 0
101 and over	35	3 5

nostic If hookworm is also present its eggs will be found in the early stages of segmentation In stools that are several days old the larvae that are found may be either hookworm or Strongyloides The advantage of a fresh stool specimen for diagnostic examination is obvious Duodenal aspirates are sometimes positive when stool examination fails to reveal larvae Sedimentation of the stool will often detect light infections missed by simple smear examination Strongyloides eggs are rarely found except in purged stools

Prognosis is favorable except in exceedingly heavy infections involving hyperinfection which may be accompanied by other debilitating diseases

Treatment Gentian violet tablets with a 1½ hour enteric coating are moderately effective The adult dose of 0 065 gm is given orally with meals three times daily for seventeen days As parasitic females deep in the intestinal mucosa are difficult to reach and migrating larvae and adults elsewhere in the body are not affected by oral medication it is often necessary to repeat the therapy Abdominal pain nausea vomiting diarrhea and constipation not infrequently accompany gentian violet therapy but unless severe intolerance is encountered the patient should be encouraged to continue treatment

A cyanine dye Vanquin given orally at the rate of 0 050 gm three times a day at meal times for seven days has recently been tried with considerable success Nausea is encountered during therapy with Vanquin and vomiting and diarrhea may occur Dithiazanine given by mouth in a dosage of 200 mg three times a day for twenty one days is reported to have cured 92 per cent of a group of adult patients

Prevention consists of sanitary disposal of human excretia wearing shoes and treatment of detected infections

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Ascariasis

Etiology Ascariasis is caused by *Ascaris lumbricoides* man s largest intestinal roundworm which has been one of his closest companions since the Stone Age

In ancient times when man was distinguished from other animals only by his upright position rather than by food or sanitary habits the vast majority of men probably harbored this parasite Over the centuries as man s habits and sanitation gradually changed from those of a quadruped to those of modern man this ubiquitous parasite *has partially lost its hold on him although* Stoll recently estimated that 644 400 000 of the earth s population harbor Ascaris Some 3 000 000 in the United States especially inhabitants of the mountainous and hilly areas of the South are hosts of this persistent parasite Surveys have demonstrated 60 to 70 per cent of the children and 15 to 20 per cent of the adults in some of these rural areas to be infected A combination of soil pollution near dwellings and moderate moist climate is essential for the propagation of this parasite The practice of using night soil on growing vegetables probably contributes to the Ascaris problem in many areas especially in the Orient

Life Cycle Adult ascarides are 15 to 35 cm in length and as usual among nematodes the male is smaller and less consequential than the female They live in the small intestine of man subsisting on the intestinal content The female worm passes some 200 000 eggs per day which is an indication of the slight likelihood of an infective egg successfully reaching another human host The eggs are passed in the feces and go through an embryonic development in the soil which takes three to four weeks before the infective larval stage is complete Once the larvae are fully matured within the shell the eggs remain viable in the soil for months but do not hatch When ingested by man the eggs hatch in the upper small intestine and the emergent larvae penetrate the intestinal wall and migrate via the mesenteric lymphatics and veins to the liver vena cava right heart and pulmonary arteries to the lungs They break out of the pulmonary capillaries into the air sacs migrate up the respiratory tree crawl over the epiglottis are swallowed and in sixty to seventy five days become adult worms in the lumen of the small intestine The life span of the adult worm is approximately one year

Symptomatology and Pathology The usual infection consisting of a dozen or so worms often goes unnoticed by the host and is discovered only on a routine stool examination or by the discovery of an adult worm passed spontaneously in the stool The most frequent complaint of patients infected with Ascaris is intestinal colic or vague abdominal pains An eosinophilia is present during the larval migration but patients harboring the adult worms may exhibit little or no eosinophilia During the lung migration the larvae may produce host sensitization which results in allergic manifestations such as pulmonary

larvae have been found in the liver brain spinal cord lungs cardiac muscle kidney and lymph nodes During the migratory phase the larvae may be found in normal tissue some distance ahead of the progressive linear lesion later becoming enclosed in a granuloma Similar lesions of the retinal fold and vitreous membrane of the eye due to hookworm larvae have been reported

Symptoms To date the syndrome visceral larva migrans has been recognized only in children from one to four years of age A history of close contact with the soil dogs or cats and dirt-eating may be elecited The disease frequently follows a benign asymptomatic course characterized by a marked persistent eosinophilia of 20 to 80 per cent and hepatomegaly Intermittent fever cough anorexia failure to gain weight muscle pain joint pain abdominal pain dermatitis and neurological disturbances may be present in more severe infections Pneumonitis is occasionally present and pulmonary infiltration may be seen in roentgenograms of the chest The spleen is seldom enlarged Skin rashes on the lower extremities have been reported

A number of the children have exhibited marked anemia and eosinophilia accompanied by a high total leukocyte count There is usually a marked increase in blood globulins largely gamma globulin The liver function tests are often normal although the cephalin flocculation test may be positive The erythrocyte sedimentation rate may be elevated Albumin was present in the urine of several children The larvae of several nematodes may cause choroiditis iritis and hemorrhage A recent study of the eyes of 24 children (aged 3 to 13 years) removed because of a clinical diagnosis of retinoblastoma revealed nematode larvae

Diagnosis The diagnosis of Toxocara infections is usually established on clinical grounds with the triad of marked eosinophilia hepatomegaly and hyperglobulinemia The last named finding is of cardinal importance in diagnosis In severe infections liver biopsy and the demonstration of typical eosinophilic granulomatous lesions and larvae confirm the diagnosis Skin tests and serological reactions employing antigens prepared from various nematodes have given promising although equivocal results

The differential diagnosis may include trichinosis hepatitis eosinophilic leukemia Loeffler s syndrome familial eosinophilia miliary tuberculosis asthma whooping cough retinoblastoma endophthalmitis and liver invasion by adult *Capillaria hepatica* (nematode)

Treatment As only a few infections with visceral larva migrans have been recognized therapy is still in the experimental stage Arsenicals and the piperazine Hetrazan have been used in an attempt to kill the larvae but with disappointing results Corticotropin or adrenal corticosteroids may be of value in ameliorating hypersensitivity reactions Epinephrine may also be of value Broad spectrum antimicrobial drugs are suggested for pulmonary involvement Treatment at present is largely supportive and symptomatic including antianemic measures

Prevention Small children should be protected against contact with infected dogs and cats especially kittens and puppies which are more commonly and heavily infected Animals under six months old should be dewormed every month and older ones every two months Worms passed as a result of treatment should be destroyed Dog and cat stools passed in children s play areas should be buried and sandboxes which offer an attractive defecating area to cats should be covered when not in use There is no satisfactory chemical for killing the ova in soil

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Enterobiasis

(Oxyuriasis Pinworm or Seatworm Infection)

Etiology Enterobiasis familiar to most physicians as oxyuriasis is due to a small white worm *Enterobius vermicularis* The female worm is 8 to 13 mm in length and because of its pointed tail is named the pinworm Unlike many helminths Enterobius is not limited to the rural and the poor but is found in all urban economic

Dithiazanine is effective against Ascaris The adult dose is 200 mg three times a day for five days

Hexylresorcinol is an effective ascaricide and has been used extensively The one precaution that must be taken with hexyl resorcinol is to be certain that the intestinal tract is empty when the drug is given as it will combine with food and have little action on the parasite The dose of hexylresorcinol is 0 1 gm for each year of age up to 10 years Hexylresorcinol (Crystoids Anthelmintic) is available in pill form and should be swallowed with a little water When children are treated it is essential to see that the pills are actually swallowed and that none remain in the mouth to be chewed later since a superficial burn will be produced The patient should refrain from eating for five hours after treatment A mag nesium sulfate purge is given on the following morning to hasten the expulsion of the injured and dead worms The ascar ides are not all passed immediately after treatment but may appear in the stool over a period as long as ten days There fore the post treatment stool examination should be delayed for two weeks from the date of treatment If eggs are still present a second treatment may be given Ap proximately 90 per cent of all the ascarides are removed with a single treatment and 60 to 80 per cent of the patients are com pletely freed of their infection

Santonin is not very effective in safe doses Oil of chenopodium an effective ascaracide has caused a number of fatali ties apparently among persons who are especially sensitive to it

Prevention Prevention consists of the disposal of human excretia in sanitary privies or toilets Children must be taught to use these facilities and to avoid con tamination of hands and food with soil Fresh vegetables grown in areas where human excreta is used for fertilizer should be thoroughly washed and preferably cooked Swine harbor an ascarid mor phologically similar to the species in man but it is evidently physiologically distinct and is not a source of human infection

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Visceral Larva Migrans

Etiology The name visceral larva migrans has been given to a clinical syn drome resulting from the invasion of human viscera by nematode larvae nor mally parasitic in lower animals Dog and cat ascarides of the genus Toxocara are apparently the most common cause of the disease Aberrant human Ascaris Strongy loides and hookworm larvae may occasion ally produce the syndrome

Life Cycle The dog and cat ascarides *Toxocara canis* and *T cati* are widely distributed throughout the world Undetected human infections with their larvae are probably more widespread than the re ports from the United States England and Puerto Rico would indicate The adult female worms are 10 to 12 cm in length and produce numerous eggs which are passed in the feces of the host In moist soil the eggs become embryonated in several weeks When ingested by dogs or cats the larvae hatch in the small intestine and migrate through the in testinal mucosa and by way of the blood stream to the liver lungs bronchial tree and trachea they are swallowed again and mature in the small in testines of these animals In man the larvae hatch ing from ingested embryonated Toxocara eggs pene trate the intestinal mucosa and are carried by the blood stream to the liver lungs and other organs and there they remain as larvae seldom completing the cycle to adulthood in the intestine These larvae apparently migrate through the various organs stimulating typical eosinophilic granulomata Ex perimental evidence indicates that the larvae can remain alive a year or more in man The varied clinical manifestations may be due to the number of larvae their location and the individual patient s response to their presence One patient with a severe infection was found to harbor 60 larvae per gm of liver 5 per gm of muscle and 3 to 5 per gm of brain tissue Repeated infections with larval nema todes in abnormal hosts frequently result in the development of allergic reactions Hence the infec tion may become clinically significant in hyper sensitive individuals

Pathology The characteristic lesion has most frequently been encountered in the liver and consists of gray elevated circum scribed areas approximately 4 mm in diameter Microscopically these granulom atous lesions consist of eosinophils lympho cytes epithelioid cells and giant cells of foreign body type surrounding the larva Extensive hepatic parenchymal necrosis may be present and Charcot Leyden crys tals may be seen Eosinophilic granuloma tous lesions are numerous and are en countered in practically every organ of the body Lesions containing Toxocara

of three consecutive days will detect the majority of infections although as many as six swabs on different days may be necessary to ensure a positive diagnosis Mothers often discover the female worms on the outside of a freshly passed stool or crawling in the anal region of the child soon after he has been put to bed

Although the eosinophil count may be slightly increased in the presence of Enterobius it is of no diagnostic significance since many infected persons have normal counts

Treatment The treatment of a person harboring pinworm is frequently unsatisfactory if other infected members of the household are untreated and remain as a source of infection It is recommended therefore that all members of the household be examined by the Scotch tape swab technique and that all those found infected [illegible] treated simultaneously

The piperazine salts citrate phosphate [illegible] lipate are the drugs of choice against [illegible] obiasis and are available as a palatable [illegible] tablets or wafers for chewing (Ante [illegible] Piperazine is most effective against [illegible] rm when taken before breakfast fol[illegible] by a glass of water which carries [illegible] ug to the cecum and colon the [illegible] of the worms Therapy is continued [illegible] ven consecutive days employing the [illegible] ing dosage

[illegible] dose of Piperazine Used in Therapy of Enterobiasis

[illegible]	PIPERAZINE CITRATE SYRUP (ml)	EQUIVALENT PIPERAZINE HEXAHYDRATE (gm)
[illegible]	2 5	0 25
[illegible] 16 30	5 0	0 50
[illegible] 31 60	10 0	1 0
O[illegible] 60	20 0	2 0

The writer cured 58 of 60 patients with the seven-day course of piperazine Over dosage with piperazine may result in nausea vomiting dizziness difficulty in focusing vision and urticaria

Gentian violet in enteric-coated tablets is an effective inexpensive therapeutic agent for the treatment of enterobiasis A course of ten consecutive days of therapy is effective and relatively well tolerated even a seven day program of therapy has been reported as successful The usual adult dose of gentian violet is 0 065 gm (1 grain) three times a day before meals Children are given 10 mg per year of age thus a ten year-old would receive a total of 100 mg a day or 33 mg (0 5 grain) three times a day

Several cyanine dyes are effective on oral administration in enterobiasis Vanquin is given for five to eight days in a dosage of 0 6 to 0 7 mg per kg of body weight three times a day Dithiazanine also gives a high rate of cure after only five days of therapy at the adult dose of 100 mg three times a day Nausea and vomiting may accompany therapy with these two compounds and gentian violet

It has been shown that zinc oxide ointment liberally applied to the perianal region four times daily for 21 days results in a cure of 80 per cent of pinworm infection This regimen probably prevents reinfection and retroinfection and although it is not as effective as piperazine therapy it might be combined with piperazine therapy in refractory infections

Prevention Since poor personal hygiene plays an important part in acquiring and perpetuating the infection education concerning handwashing after toilet and before meals is indicated Thorough daily bathing of the perianal region should help reduce infection During treatment and for a week thereafter a diaper or close fitting cotton pants will prevent contamination of the hands and dissemination of the eggs The diaper or pants should be boiled daily and the bed sheets and night clothes boiled two or three times a week Dogs and cats do not harbor pinworms and hence play no part in its spread The administration of piperazine on one or two days a week is effective in controlling the infections in institutions for children

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Filariasis

Etiology Filariasis is an infection with one or more species of threadlike nematodes The adult worms live in various parts of the human body and the female gives birth to delicate elongate [illegible] (150 to

classes even in the seats of the mighty No other helminth parasite of man enjoys such an extensive geographic distribution In general children are more commonly infected than adults Negroes appear to be less susceptible to pinworm than white persons

Life Cycle The adult worms inhabit the cecum and adjacent portions of the colon and ileum where they presumably feed on the intestinal contents although it has been suggested that they may attach themselves to the intestinal wall and consume cellular material The mature female worm usually does not pass her eggs into the intestinal lumen but stores them within her body until she contains some 11 000 at which time she migrates down the colon and out the anus On reaching the perianal region the worm is stimulated presumably by the lower temperature and altered environment to expel her eggs in great numbers These eggs become infectious within a few hours Ingested eggs containing infective larvae are acted upon by the digestive juices of the upper gastrointestinal tract and the larvae are freed in the duodenum They migrate down the intestine to their site of predilection where they complete their development in as short a period as fifteen to twenty-eight days although some worms may take twice this length of time

There are several methods of transmitting pinworm infection Perhaps the most common among children is the direct anus-to-mouth transference of eggs by contaminated fingers and the contamination of food by soiled hands This source of infection may be especially important in individual reinfection as eggs are frequently found beneath the fingernails of infected children

Pinworm eggs become dislodged from the perianal region of the host and may be widely disseminated in the environment These eggs may be carried to the mouth on hands or food or may become airborne and thereby swallowed or inhaled Thus Nolan and Reardon report that 91 7 per cent of 241 dust samples collected in households with pinworm infected members contained Enterobius eggs Eggs were recovered in dust from floors baseboards tables chairs davenports dressers shelves picture frames window sills toilet seats wash basins bath tubs bed sheets and mattresses The largest number of eggs was found in bedrooms This study demonstrates how the infection may spread through families or groups living in the same environment It is surprising that any member of a family should escape infection when there are several infected persons in close association with him and in view of the large number of eggs produced by the female pinworm Pinworm eggs have been isolated from the dust of schoolrooms and a school dining room which presumably could serve as the original source of infection for children Schuffner and Swellengrebel present data suggesting that larvae may escape from eggs in the perianal region of the host and reentering the colon by way of the anus produce what they term a "retro-infection

The simple life cycle of Enterobius closely associated with man in all stages explains the ease with which it reinfects its host spreads through families and children s institutions and has assured its survival despite the elaborate sanitary facilities developed by modern man

Fortunately for man the eggs of Enterobius are relatively susceptible to climatic conditions and in a warm dry environment they survive only a few hours or days This probably explains why over 90 per cent of the eggs recovered by Nolan and Reardon in household dust were not viable

Symptoms It is not uncommon for both adults and children to harbor pinworms without noticeable symptoms Pruritus ani caused by the migrating female worms is perhaps the commonest complaint of infected persons Various observers have ascribed a number of signs and symptoms to the presence of pinworm such as poor appetite weight loss hyperactivity enuresis insomnia irritability grinding of the teeth abdominal pain nausea and vomiting but it is often difficult to prove the causal relationship of pinworm The various symptoms have been attributed to mechanical stimulation and irritation by the adult parasite by allergic reactions and by the transportation of intestinal bacteria by the pinworm to sites where they are pathogenic

The relation of pinworm to appendicitis is problematical Ashburn found Enterobius in 7 9 per cent of 2317 surgically removed appendices The worms were found as frequently in normal appendices as in those showing chronic inflammation and more frequently in normal than in acutely inflamed appendices Ashburn concluded that no cases of appendicitis oxyurica" were present in his series Other workers including Schwarz and Straub have demonstrated penetration by the worm of the appendiceal wall accompanied by a foreign body reaction and abscess formation They conclude that pinworm may be a primary cause of appendicitis Occasionally the female worms migrate into the vagina and produce an intense vulvitis They may continue their migration into the fallopian tubes and uterus and become encapsulated

Diagnosis The usual methods of stool examination used for other intestinal parasites are of little value as Enterobius eggs are usually not present in the stools The best routine method of diagnosis is by means of the Scotch tape swab A piece of Scotch tape 2 inches long is folded sticky side out over the end of a tongue depressor and pressed firmly against the perianal region The tape is then placed sticky side down on a microscope slide and examined under the low power of the microscope for the typical eggs which are characterized by a relatively thick shell flattened on one side containing a partially developed larva The swabs should be taken soon after the patient arises in the morning before bathing as the worms frequently migrate to the perianal region during the night A swab made on each

the Pacific area during World War II These recurrent attacks are characterized by funiculitis epididymitis orchitis retrograde lymphangitis of the extremities and localized areas of swelling and redness of the arms and legs Fever chills headache vomiting and malaise may accompany these attacks which last from several days to several weeks Somewhat similar acute attacks may occur at monthly or longer intervals in patients with or without elephantiasis Usually the affected extremity becomes red hot and very painful Therapy with antimicrobial drugs is usually unsuccessful indicating a verminous rather than bacterial etiology

Obstructive Filariasis Elephantiasis is the dramatic end result of filariasis Many mistakenly believe that it is the inevitable termination of every filarial infection but fortunately the grossly enlarged scrotum or leg is the exception rather than the rule Elephantiasis has been reported in 1 to 70 per cent of infected natives in various parts of the world Obstructive filariasis develops slowly usually follows years of continuous infection and is preceded by chronic edema and often by repeated acute inflammatory attacks Adenovarix hydrocele chylocele and elephantiasis of the legs scrotum arms breasts or vulva are end results Of 2595 United States marines with clinically diagnosed filariasis only 22 per cent showed objective signs other than shotty lymph nodes and only 0 2 per cent developed severe sequelae Abscesses of the pelvis of the kidney epididymis retroperitoneal tissues inguinal nodes and iliopsoas muscles may result from the dead and degenerating worms These abscesses may be sterile but frequently pyogenic bacteria are present

Diagnosis The clinical diagnosis of filariasis will depend upon a history of exposure to mosquitoes in an endemic area in conjunction with the clinical findings discussed above The blood should be examined for microfilariae by placing a drop obtained at night on a slide and examining it under the low power of the microscope for actively moving microfilariae To determine the species of microfilariae thin or thick blood smears stained with Wright or Giemsa stain will bring out the diagnostic characteristics To detect light infections 1 ml of night blood is laked in 9 ml of a 2 per cent formalin solution The sediment is examined directly or may be allowed to dry on a slide and then stained The blood of patients with clinical filariasis does not always contain microfilariae Approximately a year elapses from the time of infection until the worm matures and produces microfilariae hence during the early months of clinical inflammatory filariasis microfilariae will not be found in the blood Likewise late in the disease by the time elephantiasis is present the adult worms and microfilariae may both have died The intradermal test using Dirofilaria antigen and the complement fixation test are of diagnostic value when microfilariae cannot be found in the blood Biopsy of enlarged lymph nodes or lymphatics may disclose living or dead adult worms or the characteristic histological picture of filariasis

Treatment It is common knowledge in endemic filaria areas that rest and moving to a cool climate reduce the number and severity of the acute inflammatory attacks Diethylcarbamazine (Hetrazan) which is given orally is quickly lethal to microfilariae and either kills the adult females or permanently sterilizes them The dosage is 2 mg per kg of body weight three times daily for seven to fourteen days Headache dizziness and malaise may be encountered during therapy Numerous antimony and arsenic compounds have been tried against infections with the adult worms Arsenamide is probably the most effective yet it is somewhat toxic and 15 intravenous doses are required Antimicrobial drugs are useful in recurrent lymphangitis due to secondary streptococcal infection Streptococcal vaccines have also been advocated for this condition

The massive edema that precedes and accompanies elephantiasis of the legs may be alleviated by pressure bandaging Administration of adrenal corticosteroids to patients with elephantiasis may be followed by a diuresis and an increased number of microfilariae in the blood stream Both effects are ascribed to a lessening of the inflammatory reaction around the adult worms which allows freer lymphatic drainage from the smaller limb Various operative measures have been tried in elephantiasis The removal of the enlarged scrotum is usually successful and results in permanent cure The repair of enlarged legs attempting to provide anastomosis between the deep and superficial lymphatics is not entirely satisfactory

Prognosis In light infections prognosis is good The prognosis once elephantiasis has developed is not good unless surgery is successful

Prevention The prevention of filariasis consists of controlling mosquito breeding

350 μ) embryos known as microfilariae *These microfilariae migrate periodically* or constantly through the peripheral blood stream or skin (Onchocerca) from which they are taken up by the appropriate species of blood sucking fly Within the insect vector the microfilariae grow and metamorphose into motile infective larvae *These migrate into the proboscis sheath of* the fly and at the time of the fly s next blood meal are introduced into or near the puncture wound The infective larvae then penetrate into the skin and migrate by way of the lymphatics and blood vessels to the various sites where the adult worms *mature Approximately a year elapses* from the time of infection until the adult female *worm matures and produces microfilariae* This is called the prepatent period

BANCROFTIAN FILARIASIS

Etiology *Bancroftian filariasis is pro*duced by *Wuchereria bancrofti* which lives especially in the lymph vessels and lymphoid tissues associated with the drainage of the legs genitalia arms and breasts Blockage of the lymphatic drainage of these areas by the parasite leads to *elephantiasis* This parasite is widely distributed in tropical and subtropical areas

Life Cycle Infection is initiated when the filariform larva is deposited onto or into the skin by infected mosquitoes especially *Culex fatigans* although Anopheles Aedes and Mansonia may also transmit this parasite Little is known of the subsequent history of these larvae until they mature and the fertilized females begin discharging microfilariae The adult worms live approximately five years The microfilariae pass from the vicinity of the parent worms into the lymph vessels and thence into the visceral blood stream The microfilariae exhibit a nocturnal periodicity and are found in greatest numbers in the peripheral circulation from ten o clock in the evening to two o clock in the morning During the daytime the microfilariae are concentrated in the viscera especially the lungs A nonperiodic variety of *W bancrofti* is found on a number of Polynesian islands Microfilariae ingested by mosquitoes undergo development and reach the infective stage in ten days

Morbid Anatomy Filarial symptoms are caused by the adult worms Living worms as well as dead and degenerating ones give rise to inflammatory granulomatous lesions of the lymphatic system This lymphadenitis and lymphangitis is due largely to allergic reactions in sensitized tissues The acute inflammatory stage is characterized by edema eosinophilia obliterative endolymphangitis and vascular stasis in the vicinity of the worm A subacute stage follows with enlargement of lymph nodes and dilated sinuses surrounded by macrophages reticular cells eosinophils and foreign body giant cells The endothelium and reticular cells of the lymphatics proliferate thrombosis may occur and ultimately fibrous obliteration In the chronic stage the cellular reaction and edema are replaced by fibroblastic hyperplasia absorption and replacement of the parasite by proliferative granulation tissue and extensive lymph varices are produced The high protein content of the lymph stimulates the growth of dermal and collagenous connective tissue and gradually over a period of years the enlarged *affected parts harden producing chronic* elephantiasis The site of the obstructive in*flammation determines the part of the body* which enlarges Obstruction of the lymphatics with resultant rupture of the lymphatics of the urinary bladder or kidney produces chyluria those of the tunica *vaginalis chylocele and those of the peri*toneum chylous ascites

Symptoms Because bancroftian filariasis may run its course over many years it varies greatly in its clinical manifestations The human reaction to filarial infection is varied and manifold and it is impossible to delimit specifically the disease stages It is possible however to classify broadly the results of filarial infection into the asymptomatic inflammatory and obstructive types

Asymptomatic Filariasis In endemic areas children are exposed to infection at an early age and by the age of six years they exhibit microfilariae in their blood without experiencing symptoms referable to their infection In time the adult worms die and the microfilariae disappear without the patient s being aware of the infection On physical examination the patient may exhibit a moderate generalized enlargement of lymph nodes *especially of* the inguinal lymph nodes Blood examination discloses numerous microfilariae and a low grade eosinophilia A survey of the blood of a group from the Virgin Islands considered physically fit for military service revealed that 20 per cent of those examined were infected with filariae

Inflammatory Filariasis The inflammatory filarial infection is an allergic phenomenon due to sensitivity to the products of the living and dead adult worms Superimposed streptococcal and fungal infections may occasionally be involved Inflammatory reactions to filarial infections occurred in service *personnel one to twenty* two months after exposure to infection in

further symptoms Several courses of therapy may be required

Prevention Prevention consists of the avoidance of water courses along which Chrysops hover and the use of repellents

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ACANTHOCHEILONEMA PERSTANS

Acanthocheilonema perstans is common in Africa and is also found in South America and Dutch New Guinea The adult worms are found in the peritoneal pleural and pericardial cavities The microfilariae are found in the blood and are nonperiodic Small biting flies of the genus Culicoides serve as the vector of this nematode The adult worms cause little tissue reaction and most infections are asymptomatic Massive infection of the liver by microfilariae is reported to cause pain and enlargement of this organ Edema Calabar swellings fever malaise headache and drowsiness are attributed to the presence of this parasite Diethylcarbamazine (Hetrazan) given orally has no effect upon the microfilariae but may have a slight sterilizing effect on the adult female worms Preliminary studies in which diethylcarbamazine was given intraperitoneally are encouraging

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MANSONELLA OZZARDI

Mansonella ozzardi is found in the West Indies Yucatan Panama the neighboring coast of South America and northern Argentina The intermediate hosts are small biting flies of the genus Culicoides The adult worms live in the peritoneal cavity in the mesentery and attached fat There is no evidence that the worm is pathogenic The microfilariae are found in the blood and are nonperiodic There is no specific therapy

ONCHOCERCIASIS

Etiology Onchocerciasis is caused by *Onchocerca volvulus* the so-called blinding filaria In Africa it has a wide distribution but in America it is limited to a narrow strip of coffee growing uplands on the Pacific slope of Guatemala and Mexico and to a more recently discovered focus in eastern Venezuela It was probably imported to America from Africa in slaves It has recently been reported in South Arabia

Life Cycle The adult worms are threadlike the male growing to 4 5 cm and the female to 70 cm They live coiled in fibrous subcutaneous nodules which vary from the size of a small pea to that of an egg The adult female passes microfilariae which are found in the nodules and in considerable numbers in the skin of the host but not in the blood The microfilariae are ingested by the blackfly of the genus Simulium when it bites the skin of an infected person The nodules are found in all parts of the body In Africa the nodules are most common on the trunk thighs and arms and in the Americas on the head and shoulders Although the site of bite of the fly and deposition of the larva may partially determine the site of the nodule constriction of clothing and skin which temporarily impede the migrating worms leads to their encapsulation in these sites Some of the adult worms do not become encapsulated thereby preventing their detection

Symptoms The tumors produced in response to the presence of the adult worms are confined to the superficial connective tissue and do not invade the muscles or viscera They may be painful may itch and may become secondarily infected with pyogenic bacteria or may become cold abscesses Dermatitis is frequently associated with onchocerciasis An allergic pigmented dermatitis called mal morado" in Mexico and "erisipela de la costa" in Guatemala which most often affects the face is not uncommon An itching macular rash may develop on the body but especially on the legs In chronic infections the skin becomes thickened dark inelastic and coarse in texture The legs may become edematous and the inguinal lymph nodes enlarged The Arabs call the disease soda meaning black It may also be one cause of craw craw or gale filarienne " a dermatitis accompanied by pruritus Microfilariae can be found in skin scrapings from these lesions

Ocular involvement occurs in 10 to 85 per cent of those infected and is the most serious complication of this infection In some areas 5 per cent of those infected have marked visual impairment and become blind Photophobia irritation discomfort and conjunctivitis are the first symptoms Punctate keratitis iridocyclitis vascularization of the cornea and panus gradually develop The iris thickens becomes adherent to the anterior surface of the lens and undergoes atrophy

areas with DDT sprays Spraying the interior of houses is also a valuable control measure Screening of houses and the use of bed nets and repellents are also indicated

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FILARIASIS MALAYI

Filariasis malayi is caused by *Wuchereria malayi* which closely resembles *W bancrofti* This parasite is found in the Orient from Indonesia to India Ceylon to China The adult worms live in the lymphatic system of man The microfilariae show nocturnal periodicity although they are *also present during the daytime in some* numbers The mosquito vectors belong to the genera Mansonia and Anopheles The *symptoms and pathological changes* due to this parasite are very similar to those of Bancroft s filariasis and both acute and chronic manifestations occur Elephantiasis is common in this infection and it is preponderantly of the lower extremities less common in the arms and rare in the genitalia *Diagnosis* is made by finding the characteristic microfilariae in the peripheral blood Diethylcarbamazine (Hetrazan) is used in therapy but for some unknown reason reactions to the drug are much more frequent than among Bancroftian filariasis patients *Control* of this infection is a matter of mosquito eradication The larval forms of Mansonia mosquitoes depend upon water plants (Pistia) for air and the removal of these plants or killing them with herbicidal sprays provides a considerable degree of control

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LOAIASIS

(*African Eye Worm*)

Etiology Loaiasis is caused by *Loa loa* a threadlike worm 3 to 5 cm in length This disease is confined to west and central Africa especially along the Congo River and its branches The adult worms wander extensively throughout the human body and they have been found in many organs at autopsy However it is their migration in the subcutaneous tissues especially about the face and conjunctiva of the eye that is noticed by the patient The so-called Mango fly of the genus Chrysops which is a diurnal biter is the vector of Loa

Symptoms Loaiasis is a chronic slowly developing disease in which symptoms do *not usually occur until three years after* infection and the parasite may persist as long as seventeen years The parasite may cause considerable irritation but no serious damage Transient swellings arise which may last for a few days or a week or longer *The swellings (Calabar) arise* suddenly are painful may itch may occur subcutaneously on any part of the body and may approach the size of a hen s egg The wrists and arms are the most common sites Usually a dermatitis and an eosinophilia of some magnitude are present These temporary inflammatory reactions are considered an allergic reaction to the products of the worm Chandler produced a large swelling by the injection of a minute amount of Dirofilaria antigen into *the skin* of a Loa infected patient Similar reactions *in the region of the throat urethra* bladder and possibly other regions of the body may give rise to pain of unexplained origin There apparently is no permanent damage due to the Calabar swelling The migration *of the adult worm under the skin of the* face and beneath the conjunctiva may cause considerable pain irritation congestion swelling and lacrimation Quick relief is obtained when the *parasite migrates* to the deeper tissues

Diagnosis The diagnosis of loaiasis is often made by the patient who notes the presence of (1) Calabar swellings (2) the outline and movement of the worm beneath the skin (3) the migration of the worm to the eye The microfilariae are most numerous in the peripheral blood about midday Eosinophilia is usually marked The skin test employing Dirofilaria antigen usually gives an immediate positive *reaction*

Treatment Surgical removal of the worm from the conjunctiva under local anesthesia is effective in the treatment of loaiasis For the intense pain that the parasite causes in the region of the eye *Novocaine* should be dropped into the conjunctival sac Hetrazan 2 mg per kg of body weight three times daily for ten days kills the adult worms and microfilariae and prevents

Calcified worms remain for years as hard subcutaneous cords or may be detected deep in the body on roentgenographic examination

Diagnosis The diagnosis of dracunculosis is usually made by the patient s noting the presence of cutaneous ulcers and worms in the subcutaneous tissues Wetting the ulcer may bring forth typical larvae

Treatment Natives extract the worm by winding it on a stick a few centimeters each day Extraction takes ten to fourteen days Surgical removal using a local anesthetic and aseptic precautions is usually successful Elliott reported excellent results from the injection of a phenothiazine emulsion along the path of the worm which causes relaxation of the parasite making it possible to remove it by gentle traction Rousset s studies indicating that large doses of diethylcarbamazine (Hetrazan) are of therapeutic and prophylactic value should stimulate further investigation

Prevention In the prevention of dracunculosis wells and tanks approached by steps on which persons are able to stand in water as they obtain a supply should be altered and provided with pumps Biological control of the disease by the introduction of the fish *Barbus puckelli* which feeds voraciously on Cyclops and the guinea worm larvae has proved feasible For personal prophylaxis boiling or filtering drinking water through coarse cloth is effective

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Hookworm Disease

(Ancylostomiasis Uncinariasis Tropical Chlorosis Miner s Anemia)

Etiology Hookworm disease is a clinical syndrome caused by infection with *Ancylostoma duodenale* or *Necator americanus* Hookworm infection implies the harboring of hookworms in the intestine with or without symptoms

Life Cycle The human hookworms measure about 1 cm in length the female being slightly larger than the male Ancylostoma is slightly larger than Necator The adult worms live attached to the small intestine mainly the jejunum A female Necator produces 5000 to 10 000 eggs per day and Ancylostoma twice as many The larva develops rapidly in the egg and hatches under favorable conditions of moisture and temperature in about 48 hours The rhabditiform larva hatches from the egg shell and after two moltings within a few days becomes an infective filariform larva enclosed in a transparent sheath This larva may travel upward or downward in the soil for a few inches as changes in moisture require Its life span may be several weeks in moist soil although it does not feed as long as it retains its sheath When the skin of man is exposed to infected soil the larva penetrates rapidly enters a blood vessel and is carried to the lungs where it breaks out into an alveolus It then makes its way up the bronchi and trachea into the pharynx It is swallowed and passes into the small intestine where it develops into an adult About six weeks are required from the time of penetration of the skin until eggs appear in the stools The life span of the hookworm is several years the heavier the infection the shorter the average life span of individual worms One light experimental infection persisted for 14 years

Epidemiology Hookworm infection is endemic in many parts of the world between 36 north latitude and 30 south latitude Moisture warmth sandy or loose soil promiscuous defecation and absence of shoes are the chief factors responsible for infections A mean monthly temperature of 50 F is necessary for the development of the larvae in the soil Regions having less than 40 inches of rainfall a year may show a high incidence of light infections but rarely have heavy infections The disease is almost entirely rural except for mines where disposal of excreta is unsanitary

The hookworm belt in the United States is principally along the Atlantic and Gulf seaboards from North Carolina to eastern Texas The other important area is the southern Appalachian region including southwestern Virginia western North Carolina eastern Kentucky and eastern Tennessee Immigrants from rural Puerto Rico frequently harbor hookworm Recent surveys indicate that there has been a marked reduction in the prevalence of hookworm infection and an even greater reduction in hookworm disease in the South

Examination of returned American military personnel after overseas service especially in the Far East revealed many light infections with Ancylostoma

Morbid Anatomy The blood in heavily infected persons presents a picture of microcytic hypochromic anemia In extreme cases a picture of macrocytic hyperchromic anemia may be present There is often an eosinophilia ranging up to 25 per cent The bone marrow shows an increase of erythropoietic cells The liver may show fatty infiltration In fatal cases the small intestine usually shows some atrophy of the epithelium and increase in the connective tissue elements of the mucosa Petechial hemorrhages are found at the site of attachment of the worms The heart is dilated and its muscle is flabby There is often edema of the subcutaneous

The eyeball atrophies and with the entrance of microfilariae into the sheath of the optic nerve blindness is complete Numerous microfilariae are found throughout the structure of the eye and it is probably their secretory products and the toxins from the dead microfilariae which cause the lesions

Diagnosis The presence of subcutaneous nodules visual disturbance and ocular lesions in persons from endemic areas is suggestive of onchocerciasis Marked eosinophilia is a constant finding Very small nodules may be overlooked during physical examination and worms may be present without nodule formation Demonstration of microfilariae in the skin gives the specific diagnosis With a sharp razor blade a thin section of skin is removed from near the nodule skin lesion or from the shoulder area It is teased out with needles in a drop of water to free the microfilariae and the preparation is examined under the low power of the microscope

Prognosis The prognosis of onchocerciasis is good if the infection is detected early and adequately treated

Treatment Surgical removal of the worm containing nodules using a local anesthetic is the method of choice Diethylcarbamazine (Hetrazan) 1 to 2 mg per kg of body weight three times a day for two to three weeks is effective against the microfilariae but not against the adult worms Marked ocular and orbital inflammation and other allergic manifestations frequently result from the rapid destruction of microfilariae therefore initial total daily doses of 25 mg of diethylcarbamazine accompanied by an antihistaminic should be used Cortisone or prednisone given a day before and during the first four days of Hetrazan therapy reduces the allergic reactions Improvement of ocular symptoms and skin lesions usually follow this chemotherapy Suramin (Bayer 205) kills the adult worms and the microfilariae gradually die off in several months Suramin is given intravenously 1 gm weekly for five injections The patient should be under constant medical supervision as severe reactions may be produced

Prevention Avoidance of the vector flies is impractical as a preventive measure against onchocerciasis because the fly is a daytime biter Repellents should be used by those working out of doors in endemic areas Treatment of breeding places of the flies with larvicides has met with considerable success in Mexico and Guatemala

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Dracunculosis

(Guinea Worm Fiery Serpent)

Etiology Dracunculosis is caused by *Dracunculus medinensis* which inhabits the subcutaneous tissues and body cavities of man It characteristically produces ulcers of the feet and legs

Life Cycle The gravid female worm which grows to a meter in length migrates to the skin especially to such parts as the legs and feet which come in contact with water The worm penetrates the subcutaneous tissues and produces a cutaneous blister which ulcerates When the ulcer comes in contact with water the worm discharges large numbers of larvae These larvae are ingested by water fleas of the genus Cyclops migrate into its hemocelic cavity and mature When man or other susceptible mammalian hosts drink water containing infected Cyclops they acquire the infection Approximately a year is required for the complete development of the adult worm

Geographical Distribution Dracunculosis is an important medical problem in India and the Middle East It is locally important in Iran Afghanistan Turkestan Egypt and Central Africa Stoll estimates that 48 000 000 persons harbor the parasite The disease is associated with dry climates where there is a concentration of water supplies in step wells or reservoirs in which there is a good opportunity for Cyclops to become infected Arms feet and legs of infected persons come in contact with drinking water sources into which the larvae are shed

Symptoms The symptoms of dracunculosis appear with formation of the skin blister and consist of varying degrees of urticaria nausea vomiting diarrhea dyspnea and giddiness There is a moderate eosinophilia It is believed that these symptoms are due to the absorption of toxins excreted by the worms to form the blister The symptoms suggest an allergic reaction and are amenable to treatment with epinephrine Bacterial contamination of the ulcer may produce cellulitis and subcutaneous abscesses Joints may be involved and permanent impairment may result Bacterial infection is common when worms are mechanically extracted by the patient under the usual septic conditions

slide-coverslip preparation of an emulsion of stool in water or saline Various methods developed for estimating the number of worms in the intestine are valuable in surveys of population groups in order to determine the clinical importance of the disease in such groups These methods however are not necessary in clinical practice since all persons harboring hookworms no matter how few in number should be treated

Treatment Preparation for anthelmintic treatment is important but it should not be overdone The patient should have a liquid evening meal without fats or alcohol If the patient is constipated a thorough cleansing enema is indicated Anti hookworm drugs should be given early in the morning and breakfast should be omitted Food should be omitted for 4 to 5 hours and alcohol for 24 hours after treatment

Tetrachlorethylene is the drug of choice for the treatment of hookworm as it is safe effective and cheap Millions of patients many of them anemic and cachectic have been treated with this drug The several reports of untoward effects of tetrachlorethylene relate to giddiness inebriation and rarely loss of consciousness The only reported death was in an extremely debilitated and emaciated beggar in India Carr and his associates reported the administration of 591 000 hookworm treatments with tetrachlorethylene without untoward effects other than occasional giddiness and drowsiness Patients with hemoglobin as low as 1 5 gm per 100 ml of blood massive edema and cardiac failure have been given the full dose of the drug without untoward happenings The adult dose of tetrachlorethylene is 5 ml in gelatin capsules mixed with a little water or with a little sugar Children are given 0 06 ml per pound of body weight No purgation should be employed One treatment will remove approximately 90 per cent of the Necator A stool examination should be made two weeks after treatment and the medication repeated if necessary If an Ascaris infection is present with the hookworms Ascaris should be removed by piperazine before treatment for hookworms is given because tetrachlorethylene may stimulate Ascaris to migrate or produce intestinal obstruction

Hexylresorcinol in crystalline form in specially prepared hard gelatin capsules will remove 60 to 70 per cent of the Necator The adult dose is 1 0 gm The dose for children is 0 1 gm for each year of age up to 10 The advantages of this drug are that it is nontoxic and that it will remove Ascaris as well as hookworm The crystals will burn the mouth if the capsules are chewed and the drug combines with protein and is soluble in fat so that food must be avoided for twelve hours before and four hours after treatment *Oil of chenopodium* and *carbon tetrachloride* are both effective against hookworm but because of their toxicity they are not recommended

The recovery from the symptoms of hookworm disease and the return to normal hemoglobin levels are especially slow in persons on a diet low in animal protein and iron Iron therefore should be given in large amounts The recommended daily dosage is 1 0 gm of ferrous sulfate (exsiccated) in capsules or 6 0 gm of ferric ammonium citrate in a 50 per cent solution These preparations should be given in three divided doses after meals It is best to start with smaller doses in order to avoid intolerance Children should receive doses in proportion to their weight This treatment produces rapid stimulation of reticulocytes and increase of hemoglobin and erythrocytes with rapid general improvement of the patient Liver extract is of no value except for its iron content The diet should be abundant and well balanced but this alone will not cause rapid improvement unless it has a high iron content

Prevention The prevention of hookworms consists of ensuring the sanitary disposal of human excreta Since the hookworm larvae are unable to migrate vertically to any height the deposition of excreta in a pit privy or a bored hole latrine is sufficient to prevent infection The wearing of shoes will aid in the prevention of infection but local customs and cost often preclude their use Treatment though of great value to the patient may be only of temporary value if reinfection can take place

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tissues sometimes even of the brain and free fluid in the serous cavities

Symptoms The larvae in penetrating the skin produce lesions which are called ground itch These consist of maculo papules which become small vesicles They are often confluent and rupture dis charging serous fluid They are surrounded by local erythema and swelling Itching is severe The commonest site is on the feet particularly between the toes but in miners it may be on the arms legs or buttocks A creeping eruption type of lesion may be produced Regional lymph nodes are often enlarged especially if secondary in fection takes place

The larvae in passing through the lungs may produce bronchitis if a heavy infec tion occurs at one time It may be accom panied by fever It has been noted par ticularly among miners

The worms feed mainly on blood of which they are wasteful only fluid con stituents being absorbed Most of the in gested material is rapidly excreted through their anus Hookworms ingest from 0 026 to 0 22 ml of blood daily Ancylostoma consumes more blood than Necator In heavy infections the worms individually consume less blood than in light infec tions Although a hemolytic toxin has been demonstrated in extracts of hookworms it has not been shown that such a toxin con tributes directly to the anemia or other symptoms

Very light infections usually produce no recognized symptoms but elimination of the worms sometimes increases the vigor or accelerates normal development in chil dren Mild cases show slight pallor of the skin with a yellow tinge dryness of the skin *with decreased perspiration some* times slight abdominal discomfort slight cardiac palpitation on exertion slight weak ness of the muscles and distaste for work The appetite may be increased Bowel movements are usually normal Such cases usually show 4 000 000 to 5 000 000 erythrocytes per cu mm a hemoglobin concentration between 9 and 12 gm per 100 ml and varying degrees of eosino philia

Moderately severe cases show an exag geration of these symptoms The hair is dry and lusterless the expression of the face is dull there may be general itching of the skin the appetite may be voracious and the patient may eat earth or other mineral material although *he rarely* ad mits this The tongue shares in the general pallor and *may show atrophy* of the papillae The bowels are usually consti pated but there may be irregular inter vals of diarrhea The heart shows slight *hypertrophy the pulse is rapid and often* weak and a hemic systolic murmur is usu ally heard over the precordium Electro cardiographic studies indicate that there is *no change in the cardiac conduction mech* anism There is usually dyspnea on exer tion There may be dizziness tinnitus and headache Weakness is marked fatigue is *rapid and movements are slow* There may be a slight amount of albumin in the urine with or without a few casts There may be edema of the feet The blood contains 3 000 000 to 4 000 000 erythrocytes per cu mm The hemoglobin is between 4 0 and 9 0 gm and eosinophilia is usually present

Severe cases show further intensification of the anemia and cardiac dilatation Weakness and stupor are apparent Edema may involve the entire body including the face and the serous cavities and cardiac insufficiency may be present Slight exer tion causes severe dyspnea The reflexes may be abolished and paresthesias are present The skin is very dry The appetite may be enormous or poor with associated pica The stomach may become dilated and nausea and vomiting are frequent Diarrhea may predominate over constipa tion The stools do not contain gross blood but occult blood is readily found The urine may show albumin and casts These patients show between 1 200 000 and 3 000 000 erythrocytes per cu *mm and* 2 0 to 4 0 gm of hemoglobin The color index sometimes exceeds 1 Eosinophilia is usually present

In addition to these symptoms hook worm disease retards general development Puberty is often delayed and if it oc curred before infection took place sexual development may recede The age of the patient may appear five to ten years less than it actually is Mental development is proportionately retarded In adults im potence may occur in men and menstrua tion may cease in women

Diagnosis The most important element in the diagnosis of hookworm is to keep the disease in mind in the presence of symptoms and to examine *routinely* the feces of every patient in areas where the disease might be present The final diag nosis of hookworm infection is based en tirely upon the demonstration of ova in the stools The simplest method is by a

fertile Ascaris or hookworm eggs and result in unnecessary anthelmintic therapy

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Hirudinea

Hirudiniasis

(*Leech Infestation*)

Hirudiniasis or leech infestation may be acquired from exposure to infected lakes ponds or ditch waters and damp tropical forests Leeches vary from 3 mm in length when the immature form attaches to man to 10 cm when they are fully grown The mouths of some leeches are provided with cutting jaws Their salivary gland secretion prevents the coagulation of blood so that the wound continues to bleed after they have detached themselves

External hirudiniasis is due to both land and aquatic leeches which attach themselves to the skin of man and beast and suck blood They may invade the nostrils The wound is usually painless until the engorged leech drops off and the oozing of blood continues Land leeches found in Asia India the Philippines Australia and South America climb shrubs from which they drop on man in numbers The numerous wounds may result in considerable blood loss Secondary bacterial infection and ulceration of the wound are not uncommon Leeches should be removed with care lest the animals jaws be left in the wound Strong salt solution vinegar dropped on the site of attachment or a match flame applied to the worm will cause it to relax when it may be easily removed The wound should be washed with an antiseptic solution the flow of blood stopped and a sterile dressing applied

Internal hirudiniasis is most commonly caused by accidental ingestion of small immature leeches in raw drinking water They become attached to the buccal mucosa epiglottis pharynx upper esophagus nasopharynx vocal cords and trachea The most notorious species of leech involved is the aquatic leech *Limnatis nilotica* of fresh water ponds lakes and streams of Mediterranean countries As they grow they produce painful and dangerous obstruction of passages with epistaxis hemoptysis and hematemesis at times leading to considerable loss of blood There may be continuous coughing hoarseness aphonia pain in the nasal cavity throat and chest dyspnea and suffocation difficulty in swallowing and nausea Persons wading or bathing in infected water may suffer infestation of the urethra urinary bladder or vagina Leeches lodged in the upper respiratory passages may be cocainized and removed by gentle traction If leeches are attached to the posterior pharynx larynx trachea or bronchi the patient is placed in the Trendelenburg position before attempting to anesthetize and remove them Otherwise they may fall further into the respiratory tract and cause suffocation For leech infestation of the genitourinary tract irrigation with strong salt solution has proved of value in killing and removing the leeches Impregnation of cloths with repellents will protect against external infections and the boiling of drinking water will prevent internal infections

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Arthropods and Human Disease

The arthropods which include the insects spiders ticks mites scorpions centipedes and crustaceans are medically important as causative agents of disease mechanical carriers of pathogenic microorganisms and necessary intermediate hosts in which multiplication and development take place

Creeping Eruption

(*Cutaneous Larva Migrans*)

Etiology Creeping eruption is a dermatitis characterized by serpiginous intracutaneous lesions Among the nematode larvae the hookworm *Ancylostoma braziliense* is most commonly incriminated although other species of hookworms *A caninum Uncinaria stenocephala* and *Necator americanus* occasionally are the etiological agents *Strongyloides stercoralis may also* cause similar lesions Another nematode with larvae that cause creeping eruption is *Gnathostoma spinigerum* found in the Orient Creeping eruption due to fly larvae (*magots) is a dermal myiasis due pri* marily to the larvae of the horse bot Gasterophilus

Geographical Distribution Ancylostoma braziliense has a wide distribution in dogs and cats and *the infection of man has a similar distribution* In the United States the infection is prevalent on the eastern seaboard from Virginia to Florida and in the Gulf States Sea bathers who bask in the sun plumbers who come in close contact with larval infected soil and children who play in sandboxes *that are open to cat and dog pollution are most* commonly infected

Symptoms The infectious filariform larvae of *A braziliense* live in moist loamy or sandy soil where infected dogs and cats have defecated The larvae which are approximately 300 μ in length penetrate the skin of man but they are either unwilling or unable to penetrate the blood vessels and complete the usual larval migration *to the intestine They remain in the skin* The feet legs and hands are most commonly involved but infection of any portion of the body exposed to infected soil may occur Plumbers are most commonly *infected on their knees elbows buttocks* and shoulders There is an intense pruritus at the point of larval entry and a red papule develops Within a day or two as the larva migrates intracutaneously a narrow slightly elevated erythematous serpiginous lesion develops at the rate of a centimeter or two per day Vesicles form along the course of the lesion and scale off The lesion causes severe itching especially at night and scratching may lead to secondary infection The larvae migrate for two to eight weeks before dying and at the site of their demise a papule is formed Some patients develop a transitory patchy infiltration of the lungs accompanied by an eosinophilia *of the blood* as high as 51 per cent and in the sputum as high as 90 per cent This Loeffler's syndrome is the result of pulmonary migration of the larvae their destruction and *an allergic reaction of the host*

The lesions of creeping eruption due to Gnathostoma and Gasterophilus are cutaneous and subcutaneous and produce migratory swelling

Treatment The treatment of choice for creeping eruption due to *A braziliense* is the use of an ethyl chloride spray An area of 2 cm in diameter at the active end of the lesion where the larvae reside is frozen *for two to four minutes* The spraying may be supplemented by cold wet antiseptic dressings Injections of Fuadin into the infected areas or intramuscularly have been used with equivocal success The piperazine compounds *Hetrazan* and *Antepar* by mouth have also been used Secondary bacterial infection should be treated with suitable antimicrobial drugs

Surgical removal of Gnathostoma and *Gasterophilus larvae and other fly larvae* is the treatment of choice of these parasites

Prevention The control of creeping eruption of hookworm origin consists in avoid*ing skin contact with soil which has been* contaminated with dog or cat feces Keeping animals off beaches and from beneath houses where plumbers may work and anthelmintic treatment of dogs and cats *will prevent contamination* of the soil Children's sandboxes should be covered when not in use Skin infection with Necator and Strongyloides can be prevented by proper disposal of human excreta Gnathostoma is acquired by the ingestion of raw fish containing the larval stage of this worm

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Heterodera Radicicola

Heterodera radicicola is a small nematode parasite of the roots and stems of vegetables including radishes turnips and celery When the adult female or eggs are consumed with their vegetable host the *eggs of the parasite are found* in man's stool The eggs may be mistaken for in

DDT and 1 per cent benzene hexachloride or pyrethrum powder may be substituted for it The secondary pyoderma should be treated with antibiotics

Prevention The prevention of lousiness consists primarily in personal cleanliness and avoidance of infected persons bedding and wearing apparel Fortunately the lice of domestic animals are not attracted to man

Fleas

Pulex irritans is primarily a human flea The fleas of the cat and dog (Ctenocephalides) and of the rat and mouse (Xenopsylla) also frequent man They usually migrate over the body until a tight garter or belt obstructs their passage and here they proceed to suck blood Individuals vary greatly in their reaction to the salivary secretions of fleas Some are unaffected In those who are severely irritated raised red edematous lesions are produced Local application of camphorated phenol in mineral oil is palliative The control of fleas usually requires the destruction of the fleas of man dog and cat in the home Vacuum cleaning the rugs scrubbing the floors and removing debris will eliminate adult fleas as well as eggs and larvae Insecticidal sprays may also be used such as a 5 per cent DDT in oil The dog yard kennel and beds of cats should be sprayed or dusted with DDT The practice of rubbing DDT into the fur of these animals is very effective Care must be taken with cats because they may lick off the dust which is somewhat toxic to them

The chicken flea (Echidnophaga) called the stick tight flea attacks man especially children It can be controlled by spraying the chicken house and yard with DDT

The chigoe or sand flea *Tunga penetrans* is primarily a parasite of the pig but it frequently infests man and also dogs cats and rats This small flea approximately 1 mm in length burrows into the skin of the feet between the toes and under the nails Here the female nourished by blood grows to pea size The wound is painful ulcerates and becomes infected with various bacteria *Treatment* consists of surgical removal of the flea and aseptic dressing of the wound until it heals Dusting the feet and socks with a 2 5 per cent DDT powder will prevent infection

Chiggers, Redbugs or Harvest Mites

These minute mites attack men only during their larval stage *Eutrombicula alfreddugesi* is the common species found in the United States other species which make man miserable are found in most parts of the world

The redbug larva attaches to the skin and secretes a saliva which by a process of digestion creates a tube called a stylostome in the skin The dissolved tissue is sucked up for food In twelve to twenty four hours as this process proceeds an intense itching is produced which continues for several days A small red macule is formed at the site of attachment of each mite and hundreds may cover the feet legs scrotum and other parts of the body The *diagnosis* is made by the history of exposure in endemic areas the intense itching and finding the small red orange six legged larvae attached to the skin *Benzene hexachloride* (Kwell) or benzyl benzoate ointment is suggested for treatment Camphorated phenol in mineral oil is palliative *Prevention* consists in dusting DDT powder into clothing and wearing tightly woven clothing trouser cuffs should be stuffed into the shoe tops

Myiasis

(Maggot Infestation)

A number of species of flies deposit their eggs on foods especially overripe fruits vegetables and decaying meat Man accidentally ingests the eggs and larvae and *intestinal myiasis* results Fortunately the gastrointestinal juices usually are fatal to the larvae and they are passed in the feces The cheese skipper a fly maggot is not an unusual part of the gourmet s repast Nausea vomiting abdominal cramps and diarrhea may be caused by intestinal myiasis Fly larvae that are found in stools brought to the laboratory for various examinations are often the result of fly eggs being deposited on the unprotected stool as it awaits transportation to the laboratory

A number of flies of the genera Callitroga Sarcophaga and others which normally deposit their eggs or larvae on decaying flesh of dead animals will lay their eggs on infected wounds in odoriferous

Scabies

(*Sarcoptic Itch*)

The *Sarcoptes scabei* or itch mite is approximately 0 35 mm in length The female mite excavates tortuous tunnels in the skin and here lays her eggs and deposits her irritating excreta The young establish themselves in lateral burrows or come out of the mother s tunnel and develop their own The adults live about four weeks Although there is a new generation every three weeks the population does not increase to the astronomical numbers theoretically possible The average number of adult females in an infested person is 12 and few harbor more than 30 Scabies is world wide with a predilection for the poor crowded and unwashed The lesion is a reddish elevated tract on the surface of the skin with translucent vesicular swellings along its course The mites most commonly invade the skin between the fingers or on the hands and wrists They also invade the skin of the elbows groin breast external genitalia feet shoulder blades small of the back and other areas Sensitization plays an important part in the symptomatology for the intense itching which characterizes the disease does not begin until a month after the initial infection In seven to sixteen weeks after infection a maximum mite population of 50 to 500 may be reached and during this period the irritation increases until it disturbs the sleep and becomes continuous and unbearable Scratching leads to secondary bacterial infection and impetigo may develop The reaction to reinfection is prompt within twenty four hours there is marked local irritation and redness

Diagnosis The lesions and their distribution are characteristic It may be possible to make a definite diagnosis by removing a mite or a portion of one from its burrow with a needle Skin scrapings should be cleared in 10 per cent potassium hydroxide for microscopic examination

Treatment The treatment of scabies is most successfully carried out with an ointment or vanishing cream (Kwell) containing 1 0 per cent benzene hexachloride To ensure cure the whole body from the neck down should be treated Cannon and McRae cured 61 per cent of their patients with one application 97 per cent with two treatments and the remaining 3 per cent with three applications Benzyl benzoate lotion or emulsion is also very effective

Prevention The prevention of scabies consists in avoiding contact with infected persons soiled bed linen and public towels Infected bed mates should be treated The mange mites of dogs cats and other mammals may invade man s skin but apparently cannot continue their life cycle there Pet dogs and cats with mange should be treated

Pediculosis

(*Head Body and Pubic Lice*)

Man provides food and shelter for two genera of lice *Pediculus humanus* var *capitis* infests the head and *P humanus* var *corporis* the body and clothing *Phthirus pubis* usually lives in the pubic area but on occasion extends its range to the axilla chest hairs and even the eye brows and eyelashes The eggs called nits of the head and crab louse are attached to the hairs of the host while the body louse attaches its eggs to the clothing of the host All three lice suck blood for nourishment Their saliva injected during feeding and probably their excreta are responsible for the irritating roseate papular dermatitis Scratching may lead to secondary bacterial infection with crusts and matted hair Induration and pigmentation of the skin may be present in severe infestations Enlargement of the lymph nodes especially the postauricular group is present in severe capitis infestation *Phthirus pubis* infestation of the eyelashes leads to blepharitis The cutaneous lesions and characteristic scratching suggest the diagnosis which is confirmed by finding the eggs or adults The latter can be combed out of the hair with a fine toothed comb

Treatment In the treatment of head lice an ointment of 1 0 per cent benzene hexachloride in vanishing cream (Kwell) should be rubbed on the scalp thoroughly This treatment is also effective for pubic lice when the ointment is massaged into the skin of the infested area Lice and eggs should be removed individually from the eyelashes Body lice are destroyed by sterilizing the clothing by heat and using the ointment on infested areas of the body A 10 per cent DDT in pyrophyllite dusted onto the head body and clothing without undressing is highly effective Lice in Korea and Egypt have developed resistance to

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discharges Chrysomyia Wohlfartia and others deposit their eggs and larvae on fresh wounds and feed on living tissues Vomitus or odors from natural cavities with a discharge attract them to the mouth nose ear or vagina The damage done by a heavy infestation may be extensive dis figuring and even fatal Sheep and horse bot flies Hypoderma Oestrus and others may lay their eggs in the eye nose and mouth of man Flies occasionally lay their eggs on healthy persons especially babies sleeping out of doors and the larvae pene trate the skin Boil like lesions may be pro duced Dermatobia larvae penetrate the skin of the body face and neck when insects upon which the fly fastens its eggs feed on man

A cutaneous creeping eruption grossly similar to that produced by *Ancylostoma braziliense* is caused by the fly larvae of Gasterophilus the horse warble

Treatment consists of surgical removal of fly larvae when possible Irrigation of infested cavities with chloroform aids in the removal of larvae Tetrachlorethylene and purgation are useful in intestinal myiasis

Prevention consists of avoiding spoiled food on which fly eggs may have been laid bandaging open wounds and protecting sleeping babies against flies

Venenating Arthropods

(Centipedes Scorpions Spiders Ticks Wasps Ants Blister Beetles Caterpillars)

The venenating arthropods which injure man by bites stings and contact include centipedes scorpions spiders ticks bees wasps ants blister beetles and the cater pillars of moths and butterflies

Centipedes have a pair of hollow fangs" through which a venom is introduced into the victim when they penetrate the skin Small species produce only local inflamma tion The large tropical forms cause local necrosis at the site of bite lymphangitis fever vomiting and headache

Scorpions are armed with a single curved caudal stinger with which they inject their neurotoxic venom The smaller species produce a painful inflammation at the site of the sting The larger species cause pain ful local inflammation salivation nausea vomiting headache dizziness perspiration rapid respiration weakened pulse and pan creatitis Sugar is frequently found in the urine and albumin may be present *Fatal stings* usually among small children are characterized by convulsions coma and death from respiratory failure or pulmonary edema *Treatment* consists of a tourniquet on the injured member An ice pack will slow the dissemination of the toxin Spe cific antivenin is recommended Subcu taneous injection of Novocaine and epi nephrine at the site of the sting relieves the pain Phenobarbital in massive doses is helpful in stopping convulsions Spray ing DDT or benzene hexachloride on the haunts of scorpions will reduce their num bers

Spiders use venom to paralyze their prey Several species can penetrate man s skin but of these only a few can cause serious symptoms The bite of the large taran tulas of the tropics produces mild to severe pain in man *Loxosceles laeta* of South America causes extensive tissue sloughing at the site of its bite Bites of *Lactrodectus mactans* the *black widow spider* may cause severe symptoms The female black widow spider is approximately 13 mm in length and is completely black except for variable orange red markings on her body The diagnostic marking of the female is an hourglass shaped marking on her ven tral surface This species is found from southern Canada to Chile and other species are found in Europe and other parts of the world The spider inhabits lumber and junk piles camps basements and outbuild ings Outdoor privies lead as a source of bites and the buttocks and penis bear the brunt of the attacks

Symptoms The venom injected is prob ably a toxalbumin and it affects the nerve endings It is not hemolytic Frequently the bite is unnoticed but it may be painful An area of pallor reddening or urticaria may mark the site Systemic symptoms vary and are usually much more severe in children than in adults The patient becomes weak dizzy nauseated and per spires profusely Boardlike rigidity and spasm of the abdominal muscles fever and leukocytosis simulate the presence of an acute abdominal disease The blood pressure rises and breathing becomes labored Profound shock delirium urinary retention and in small children convul sions may lead to death within forty-eight hours Recovery is rapid as the toxin is excreted and is accompanied by slight fever diaphoresis and leukocytosis

Diagnosis The history of spider bite if elicited is most valuable and the gradual spread of the muscular pain is of assistance

in separating it from acute surgical abdomen

Treatment The patient should be placed in bed and given intravenously 10 ml of a 10 per cent calcium gluconate solution Antivenin is available and of value Hot baths may relieve pain and morphine may be required for analgesia Corticotropin and adrenal corticosteroids afford prompt symptomatic relief Neostigmine and d tubocurarine are both useful in relieving muscular spasm

Prevention Thorough spraying or dusting the habitats of predilection of Latrodectus with DDT affords considerable protection Special attention should be given to outdoor privies

Ticks introduce a poison into the skin along with their saliva when they feed on man Fever ascending motor paralysis and death through cardiac and respiratory failure may result The most serious disease is produced by the engorging female tick on the back of the neck or at the base of the skull The condition is most common in females as their long hair hides the attached tick Recovery takes place in one to six days after the tick is removed or falls off Gentle traction on the tick rather than a sudden jerk is recommended for removal of the ticks from the skin Freezing the ticks with ethylchloride or applying a lighted cigarette to their rear assists in their removal intact

Bees, Wasps and Ants Bees and wasps have a posterior sting apparatus the modified ovipositor through which the venom is injected into the skin Usually local inflammation and pain are the only symptoms and they disappear after a few hours Stings from a swarm of bees may be rapidly fatal Hypersensitive persons may experience a severe reaction from a single bee sting in some instances with fatal termination Such persons manifest symptoms of anaphylactic shock with respiratory and cardiac impairment edema and urticaria Prednisone 30 mg along with a quick acting antihistamine should be given immediately after exposure and this dose repeated in fifteen to thirty minutes if symptoms appear Epinephrine is also indicated Patients who have had serious reactions to bee stings should be desensitized by a course of bee antigen to prevent subsequent serious reactions An antihistamine may relieve discomfort Several species of ants produce a painful sting The "fire ant which is spreading in the southern United States causes a fiery sting and pruritic vesicles

Blister Beetles of which the Spanish fly is a well known example secrete a vesicating substance cantharadin which on contact with the skin produces a blister Some of these acute vesicating lesions heal slowly Soothing alkaline lotions are palliative

Caterpillars of moths and several butterflies have hollow venom-containing hairs Poisoning may be caused by contact with the caterpillars their nest or their windblown hairs The pain from the lesion produced by a poisonous caterpillar falling on the skin may be excruciating A vesicular erythema with a localized area of necrosis develops Windblown hairs produce a prickling and burning sensation of the skin and a severe inflammation of the eye Calamine lotion or ammonia solutions are palliative

Arthropods as Mechanical Carriers of Disease

The common housefly and its relatives the stable fly green bottle blue bottle blow fly and flesh fly breed and feed on human and animal feces and garbage Typhoid fever bacillary dysentery infant diarrhea amebiasis and cholera may be transported on the fly s body from the feces of man to his food The pathogenic organisms are also found in the vomitus and feces of flies Flies of the genus Musca are attracted to sores and food remnants on children s faces and participate in the transmission of trachoma and purulent conjunctivitis Flies have also been found to harbor the virus of poliomyelitis It is possible that fecal feeding flies may transmit infectious hepatitis The stable fly contaminated with horse manure may introduce tetanus and anthrax spores into the skin Small flies called eye gnats have been incriminated in epidemics of acute conjunctivitis or pink eye and may transmit yaws

Control of flies in addition to sprays of 10 per cent DDT in kerosene and other sprays assists in the prevention of fly breeding Garbage cans should be tightly covered and the garbage when collected incinerated or disposed of in a suitable land fill Barnyard manure should be protected against flies Houses food cabinets and milk producing barns should be screened Outdoor privies should be con

structed in such a manner as to prevent the access of flies to the feces and the pit should receive generous application of DDT spray quick lime or crude oil

Cockroaches, through their contact with filth and food may transmit pathogenic intestinal bacteria certain viruses and protozoan cysts Cleanliness in the kitchen and protection of stored foods are essential in the control of cockroaches Closing crevices around pipes running from floor to floor in apartment houses will help to keep the neighbors cockroaches at home Ten per cent DDT powder or 1 per cent benzene hexachloride powder spread about the haunts of cockroaches is an effective control measure

Bedbugs (genus Cimex) are reddish brown wingless and have a disagreeable odor The bite of the bedbug ordinarily produces red itching wheals Sensitive persons experience considerable urticaria but some persons show no reaction Although the blood sucking habits of the bedbug would seem to fit it ideally for disease transmission and although man universally dislikes this insect and desires to incriminate it in disease transmission all attempts to do so have failed Bedbugs have been infected in the laboratory with numerous organisms pathogenic for man but apparently in nature they do not spread them to any extent A 5 per cent emulsion of DDT or 1 per cent benzene hexachloride spray on infested bed frames furniture and wall crevices will control this insect

Arthropod Intermediate Hosts

The diseases for which arthropods serve as vectors and hosts in which the pathogenic organisms multiply or undergo development are considered in other sections of this book

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DISEASES OF UNPROVED ETIOLOGY

Sarcoidosis

(*Hutchinson s Besnier s Boeck s Heerfordt s Schaumann s Jungling s Syndrome or Disease Benign Lymphogranulomatosis Uveoparotid Fever Lupus Pernio*)

Definition Sarcoidosis is a systemic granulomatous disease or possibly a group of diseases of unknown etiology The disease most often involves lymph nodes lungs liver spleen skin and eyes but any tissue or organ may be affected The characteristic histological lesion consists of epithelioid cell tubercles with little or no necrosis Clinical manifestations are dependent in large part upon the degree of functional alteration produced in a particular tissue or organ and are therefore subject to marked variation Although the course may be characterized by acute clinical exacerbations or by spontaneous and complete recovery persistence of indolent disease for years is seen more often Less frequently the disease may follow an unrelenting progressive course terminating fatally

Etiology There is at present no general agreement as to a specific etiological agent in sarcoidosis It is not unlikely that several etiological agents may produce diseases which are at present indistinguishable histologically from sarcoidosis Indeed the close similarity of certain features of sarcoidosis and tuberculosis histoplasmosis coccidioidomycosis and berylliosis has prompted much of the etiological investigation to date Moreover the ability of certain microbial agents foreign bodies and chemicals to produce a lesion closely resembling the sarcoid tubercle has necessitated a clear distinction between the frequent occurrence of local sarcoid tubercles and the systemic disease

Major interest until recently has centered on *Mycobacterium tuberculosis* as the causative agent It has been postulated that sarcoidosis is either an attenuated form or a distinct clinical phase of tuberculosis Support for this hypothesis is predicated upon the occurrence of sarcoidosis as a noncaseating anergic tuberculosis in which rapid and complete bacillary destruction ensues The release of tuberculin stimulates an immunological host response which results in the production of tuberculin neutralizing substances As a direct consequence of these tuberculin neutralizing substances relative tuberculin insensitivity is present hence the concept of positive anergy Weighing strongly against this concept are the normal survival of certain tubercle bacilli (BCG) in patients with sarcoidosis the presence in similar frequency and amount of tuberculin neutralizing substances in normal subjects and the demonstration that relative cutaneous hyposensitivity in sarcoidosis is not specific for tuberculin Furthermore recently demonstrated epidemiological inconsistencies between tuberculosis and sarcoidosis have removed tuberculosis from prominent consideration as an etiological agent in sarcoidosis

Epithelioid cell granulomata may be produced in normal animals by injection of pine pollen or chemical fractions derived from pine pollen An etiological role for pine pollen in clinical sarcoidosis is however not yet established

Berylliosis has been noted to have many features in common with sarcoidosis and the possibility that beryllium present in the soil is responsible for sarcoidosis has been given serious consideration Foreign body reactions due to silica quartz talc etc may result in local sarcoid lesions but no etiological relationship of these particulate materials to sarcoidosis has been established Recently however calcareous spar has been isolated from lesions of sarcoidosis and renewed interest in this component of certain soil types has occurred

Epidemiology Sarcoidosis occurs at all ages from childhood to old age the greatest number of cases being recognized between the ages of twenty and forty The sexes are affected equally There is no indication of communicability or an inherited predisposition although the disease has occasionally occurred in siblings identical twins and household contacts

Major clinical interest in sarcoidosis has centered in the United States England the Scandinavian countries France Switzerland and Germany yet the disease is believed to occur in all regions of the world Sufficiently comprehensive and accurate prevalence data are not yet available for populations at large An attack rate of 0 66 per 100 000 has been reported for the general population of Oxfordshire England In the United States and Swiss military personnel however 2 1 and 13 cases of sarcoidosis respectively were recognized in each 100 000 surveyed One might anticipate a higher incidence in military groups because of the age selection Nevertheless these data probably represent falsely low attack rates for their respective populations since many cases of sarcoidosis might easily have escaped detection because of present inadequacies in mass diagnosis

A striking geographical concentration of sarcoidosis in the southeastern United States was demonstrated in a study of the distribution by birthplace of military personnel with sarcoidosis of World War II This distribution has been found to correlate with the occurrence of certain soil types The similarity of this geographical distribution and that of urinary calculi has also been noted A similar study of 1194 cases of sarcoidosis diagnosed at United States veterans hospitals between 1949 and 1954 not only confirmed the above geographical concentration but also extended the distribution pattern to the New England and North Central States The correlation of this latter distribution with that of forested areas is impressive The full epidemiological significance of these data is not yet clear but the predisposition of the American Negro to sarcoidosis was amply confirmed Though all races are known to be affected by sarcoidosis a ratio of Negro to white cases of 18 1 and 12 1 was encountered for the military personnel and veterans respectively In addition these studies also re-emphasize a universal finding the higher incidence of the disease in those born in rural areas

Morbid Anatomy No single histological feature may be regarded as pathognomonic for sarcoidosis A heterogeneous group of diseases or agents may simulate sarcoidosis or the local sarcoid lesion

The epithelioid cell granuloma or tubercle the cardinal feature of the disease is a discrete concentric arrangement of elongated epithelioid cells The size and development of the granulomas in a particular organ are often so similar that the pattern has been referred to as "monotonous Giant cells of the Langhans and foreign body type are common and may contain inclusion bodies such as the asteroid or spiculated bodies and Schaumann bodies (round or oval noncrystalline concentrically laminated inclusions) Neither inclusion body is specific for sarcoidosis As the sarcoid granuloma matures a fine rim of fibroblasts encircles the lesion Necrosis is infrequent but when present is acellular central and fibrinoid in character Caseation necrosis does not occur Healing takes place primarily by fibrosis with subsequent formation of a dense scar as the tissue becomes compact and hyalinized

Pathological Physiology Constitutional manifestations are produced almost entirely through mechanical interference by epithelioid granulomas and fibrous scars with the normal function of a particular organ Moreover the particular organ function which has been altered largely determines the seriousness of the disease *i e* myocardial pulmonary central nervous system or ocular lesions may be of far greater consequence than extensively disseminated lesions in less critical tissue

Involvement of peripheral *lymph nodes* is demonstrable by palpation or biopsy in almost all patients with sarcoidosis but rarely produces symptoms Deep lymph node involvement is frequent but also is unlikely to cause symptoms Enlarged hilar or peribronchial nodes may occasionally produce obstructive phenomena atelectasis and possibly together with bronchial mucus membrane involvement stimulate cough

Pulmonary involvement next to lymphatic tissue in frequency of involvement is characterized by infiltration of the interalveolar walls by the sarcoid granuloma which as it heals is replaced by fibrous tissue Intervening normal lung parenchyma undoubtedly accounts for the paucity of pulmonary symptoms until an advanced stage is reached The dense interalveolar scar tissue and reduction in the effective diffusing surface by sarcoid displacement of alveolar space make gas diffusion more difficult This "alveolar-capillary" block accounts in large part for the dyspnea and cyanosis both of which may be initiated or exaggerated by exercise

Involvement of the *heart* is usually a consequence of extensive pulmonary sarcoidosis and fibrosis leading to the subsequent development of cor pulmonale Di

rect invasion of the myocardium with displacement of myocardial fibers occurs in about 20 per cent of autopsied cases however and may lead to sudden death Thus myocardial damage in sarcoidosis may result in right ventricular enlargement progressive myocardial failure or conduction defects

Sarcoidosis of the *liver* is recognized by needle biopsy or at autopsy in approximately 65 to 75 per cent of cases yet clinical evidence of involvement of the liver is usually limited to hepatomegaly and rarely jaundice Splenomegaly is detected at autopsy in a similar percentage and also in the same frequency clinically as hepatomegaly (in about 20 to 25 per cent of cases) Secondary thrombocytopenic purpura Banti s syndrome spontaneous rupture hemolytic anemia hypersplenism and a sensation of heaviness in the splenic area have all been attributed to sarcoidosis of the spleen

Although the most extensively described manifestation the relative frequency of *cutaneous* lesions in sarcoidosis has decreased because of the wider recognition of the systemic component of the disease The small and large nodules and the diffuse flat plaques occur in about 40 per cent of sarcoidosis Despite the many and varied appearances of the cutaneous lesions the histological picture is characteristic of that seen elsewhere The lesions may persist for prolonged periods only to heal without residue or as atrophic depigmented scars New emphasis has been placed upon the occurrence of erythema nodosum in sarcoidosis The frequent association with generalized lymphadenopathy in particular with massive bilateral hilar node enlargement has been noted recently

Iritis and iridocyclitis usually bilateral are the most common *eye* lesions The fate of these lesions is quite variable there may be spontaneous complete healing but permanent progressive damage frequently resulting in blindness may be the ultimate outcome Of the unfavorable results cataracts secondary glaucoma phthisis bulbi optic atrophy and corneal opacities are the more serious sequelae

Localization in *bone* is probably more common than is determined by roentgenographic studies Diffuse granulomatous infiltrations of the marrow may occur but only those leading to resorption of cancellous bone account for the reticular lacelike pattern and punched out areas seen in the roentgenogram The cortex is rarely invaded and joint involvement is not common External evidence of bone infiltration is usually limited to a mild painless fusiform swelling of the fingers extensive destruction with multilation of the digits is infrequent

Sarcoidosis may involve any part of the *nervous system* Encephalitis convulsions and diabetes insipidus due to hypothalamic or pituitary lesions have been attributed to sarcoid lesions in the central nervous system Probably the most common lesion is Bell s palsy usually unilateral and transient in nature but sometimes followed by persistent facial nerve paralysis Several other cranial nerve lesions have been described Meningeal and cord lesions have been observed but are infrequent

Renal insufficiency may occur usually attributable to the hypercalcemia and consequent nephrocalcinosis seen in sarcoidosis Less frequently renal damage occurs as a direct result of sarcoid infiltrations

Symptoms Outstanding among the clinical features of sarcoidosis is the striking disparity between the mildness or absence of symptoms and the extensive involvement of the organs and tissues Nonetheless both constitutional reactions and local complaints referable to specific organ involvement usually occur at some time in the course of the disease They may become manifest singly in combination or in sequence making a concise clinical description difficult

Weight loss easy fatigability and malaise appear insidiously and may be accompanied by vague thoracic or abdominal complaints night sweats and low grade fever Fever is usually absent during the chronic stabilized phase of the disease and when present may be attributed to a secondary complication Nevertheless during exacerbations or in certain clinical forms of sarcoidosis such as uveoparotid fever a slight temperature elevation is frequent and in rare instances fever is the most prominent feature of the disease

Symptoms directly referable to specific organ involvement are expressed clinically in terms of functional impairment Most frequent are the symptoms related to involvement of the lungs intrathoracic lymph nodes skin and eyes

The mere presence of symptoms in pulmonary sarcoidosis signifies extensive involvement of the lungs Cough is mild transitory and intermittent but may become severe and persistent Sputum if present at all is nonpurulent and small in amount unless secondary infection or less frequently bronchiectasis appears as a complication

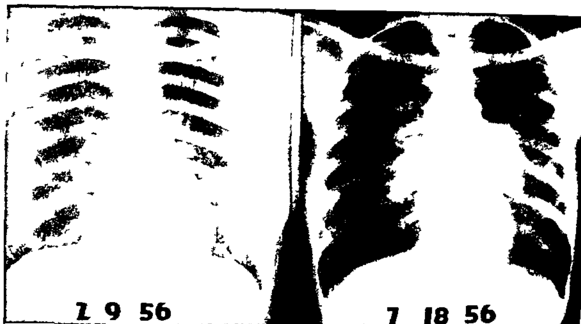


FIG 43 Asymptomatic onset of massive bilateral hilar and mediastinal lymphadenopathy (Courtesy Dr H S Weens)

Dyspnea initially mild and present only after exertion may reflect the advancing functional inroads of progressive diffuse pulmonary sarcoidosis Pulmonary fibrosis reduction of the alveolar diffusing surface by interalveolar granuloma and emphysema may further accentuate the dyspnea In addition cor pulmonale is a frequent consequence of the severe pulmonary damage and the symptoms of heart failure may be superimposed and often predominate Other symptoms of pulmonary sarcoidosis are less common mild chest pains are ill defined and may be the result of pulmonary hypertension Pleuritic pain and pleural effusion are rare

Ocular manifestations are commonly expressed in terms of difficulty in vision although mild pain may occasionally be present When severe pain occurs in ocular sarcoidosis secondary conditions such as *glaucoma usually are present*

An infrequent but well documented clinical expression of sarcoidosis is presented by the triad of uveoparotid fever uveitis relatively asymptomatic swelling of the parotid and other salivary glands and Bells palsy This triad is *rarely seen* however as the sole expression of sarcoidosis An annoying symptom dryness of the mouth may occur as a consequence of interference with salivary gland secretory function The acute phase of the disease represented by uveoparotid fever lasts from several weeks to a few months and is terminated by spontaneous regression The ocular manifestations are the least likely to clear completely and tend to relapse or recur

The *physical examination* often uncovers features which are highly suggestive of the disease Peripheral lymph nodes are usually palpable at some period in the course of almost all patients The nontender firm discrete movable nodes infrequently exceed 3 cm in diameter and are most apt to be prominent early in the course of disease or during acute exacerbations During the chronic less reactive phase the nodes may regress markedly Ocular lesions often the earliest detectable manifestation of sarcoidosis *are found in about* one third of the cases These lesions vary widely for almost any part of the eye may be affected conjunctivitis scleral nodules iritis granular uveitis posterior synechiae vitreous opacities chorioretinitis and optic atrophy alone or in combination may occur in one or both eyes *Cutaneous lesions are* polymorphic on observation but quite characteristic of sarcoidosis on histological examination Small discrete nodules and larger nodules are found over the "butterfly area of the face nose ears shoulders extensor surfaces of the extremities and trunk *Finely granular* infiltrative plaques classically described as lupus pernio subcutaneous lesions of the Darier Roussy type and erythema nodosum are other clinical variants The atrophic scars which result from the healing process are often prominent Nontender relatively *asymptomatic enlargement of the parotid* or lacrimal glands may be present Conduction

defects arrhythmias or congestive heart failure may be detected in myocardial damage from sarcoidosis Physical examination of the lungs is usually characterized by a paucity of findings Abdominal examination reveals nontender firm hepatomegaly and splenomegaly in about one fourth of sarcoidosis patients Serous effusions and joint involvement are rare in sarcoidosis

Laboratory findings are neither pathognomonic nor sufficiently constant to be of great diagnostic value Among the hematological abnormalities leukopenia moderate eosinophilia and slight monocytosis are not uncommon An unexplained mild hypochromic microcytic anemia is occasionally observed hemolytic anemia or thrombocytopenia has been described in association with splenomegaly The erythrocyte sedimentation rate is often elevated Hypergammaglobulinemia occurs in about two thirds of patients with sarcoidosis and may or may not produce elevation of the total serum protein An increase in serum alkaline phosphatase usually not correlated with bone or hepatic disease is frequently observed Hypercalcemia not necessarily associated with hyperglobulinemia or bone changes is not uncommon and usually moderate in degree although levels of 16 8 mg per cent have been reported The serum phosphorus tends to remain normal

Roentgenograms of the chest are an invaluable aid in the detection of sarcoidosis Bilateral hilar lymph node enlargement is frequently the earliest recognizable abnormality (Fig 43) Infiltration of the lung parenchyma may not be detectable in the early stages but later is seen to extend from the hila in reticulated strandlike areas Extensive nodules of variable size may be present throughout both lung fields sometimes simulating the more uniform pattern seen in miliary tuberculosis (Fig 44) The enlarged lymph nodes and the pulmonary infiltration may regress or both lesions may progressively increase The parenchymal lesions seldom coalesce although patchy apparently coalescent densities are seen in the mid lung field in advanced diffuse pulmonary infiltration Severe pulmonary fibrosis with emphysematous bullae may be the only remaining findings in the advanced stage of the disease (Fig 45) Although not diagnostic some roentgenographic lesions of sarcoidosis are highly suggestive such as enlargement of bilateral hilar and intrapulmonic nodes in the absence of anterior mediastinal nodes

Localization in bone as determined radiographically is seen in less than 10 to 15 per cent of patients with sarcoidosis The middle and distal phalanges are the most common sites and the proximal phalanges metacarpals metatarsals and others are occasionally involved The circumscribed bone lesions leave a punched out appearance without reactive changes Multiple diffuse areas of rarefaction with a reticular or lacelike pattern may be present

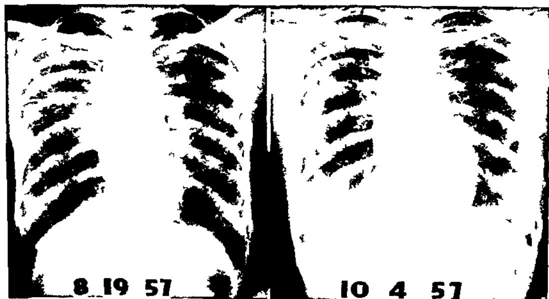


Fig 44 Diffuse bilateral pulmonary infiltration simulating miliary tuberculosis in an asymptomatic patient rapid clearing without therapy (Courtesy Dr H S Weens)

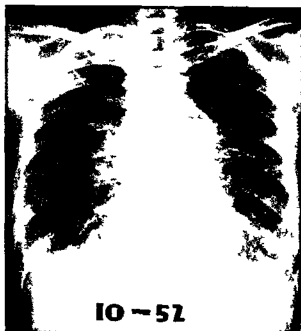


FIG 45 Advanced pulmonary fibrosis with little evidence remaining of the initial lesions of sarcoidosis (Courtesy Dr H S Weens)

Relative *tuberculin anergy* is a nonspecific characteristic of sarcoidosis as the defect apparently applies to other antigens which produce reactions of the delayed hypersensitivity type Approximately two thirds of patients with sarcoidosis have negative reactions to second strength tuberculin (0 005 mg of PPD or 1 0 mg of O T) The patients with sarcoidosis who do have a positive tuberculin test react least often to first strength tuberculin (0 00002 mg of PPD or 0 01 mg of O T)

The *Kveim* reaction is performed by the intracutaneous injection of an antigen prepared as a 10 per cent saline suspension from lymph nodes of patients with sarcoidosis After a latent period of several weeks rarely as long as a year a small papule develops which histologically is indistinguishable from cutaneous sarcoidosis The occurrence of the papule and preferably the histological demonstration of non necrotic epithelioid cell granulomata constitute a positive test Widespread adoption of the Kveim reaction has been hindered by the lack of a standardized antigen the frequent delay in evolution of the papule occasional severe local reactions and the slow resolution of the papule Nevertheless the Kveim reaction is a valuable aid in confirming the diagnosis of sarcoidosis as false positive reactions occur in less than 6 per cent under proper conditions During the less active stages of sarcoidosis false negative tests may occur The lack of absolute specificity of the reaction is suggested by the production of a similar reaction in sarcoidosis with a number of antigens obtained from sources apparently unrelated to sarcoidosis

Diagnosis Correlation of clinical findings and pathological changes is often necessary before the diagnosis of sarcoidosis can be made with confidence Sarcoidosis may be diagnosed without difficulty however in the patient with an insidious onset of mild symptoms characteristic organ involvement hyperglobulinemia negative tuberculin test compatible roentgenographic changes in the lungs or bones and biopsy confirmation of non necrotic epithelioid cell granulomata in the tissues Some features of the organ involvement strongly suggest the diagnosis even as isolated findings Among these are (1) the presence of symmetrical purplish indolent nonulcerative skin lesions or the classic lupus pernio with infiltrative plaques over the nose face eyelids and ears etc (2) the unexplained occurrence of uveitis or iritis with or without asymptomatic swelling of the lacrimal and salivary glands or transient cranial nerve paralysis (3) bilateral massive mediastinal *or paratracheal node involvement in an apparently* healthy patient and (4) nephrocalcinosis with hypercalcemia and a normal serum phosphorus Difficulty in differential diagnosis usually arises when inaccessible lesions of the internal viscera occur as the only expression of the disease

The exclusion of berylliosis Hodgkin s disease the lymphomas tuberculosis and known causes of systemic granulomatous disease should be routine in the diagnosis of sarcoidosis Some characteristics of sarcoidosis are particularly helpful in this regard Lacrimal and salivary lesions not uncommon in sarcoidosis are very rare in tuberculosis berylliosis or histoplasmosis Lesions attributable to berylliosis have not been recognized in the eye Involvement of the heart skin or bones by lesions similar to those frequently seen in sarcoidosis is now quite rare in tuberculosis in contrast tuberculosis not infrequently involves the *pleura peritoneum pericardium* and adrenal glands sites which are rarely involved in sarcoidosis The hyperglobulinemia of tuberculosis is most often characterized by a rise in alpha 2 globulin whereas gamma globulin elevation is present in sarcoidosis The insidious onset mild symptoms infrequent occurrence of fever and common occurrence of spontaneous recovery contrast sharply with the expected course of Hodgkin s disease the lymphomas and to

a much lesser extent tuberculosis

Enlarged lymph nodes or cutaneous lesions may not be available for confirmation of the diagnosis by biopsy but the small lymph nodes in a scalenus anticus fat pad biopsy frequently contain the characteristic lesions Pulmonary biopsy is rarely necessary although it is quite reliable The large number of conditions which produce nonspecific granulomas of the liver lessen the value of needle biopsy of the liver but this is an important diagnostic procedure Lastly the Kveim reaction is a means of artificially inducing the characteristic histopathological changes in patients with sarcoidosis biopsy of which affords confirmation of the diagnosis

Course and Prognosis The clinical course of the individual patient is unpredictable The time of onset is infrequently established because of the insidious nature of the disease and progress is rarely reflected clinically before the occurrence of severe functional impairment The course may be marked by remissions and exacerbations persistence without evident change unrelenting progressive functional impairment or spontaneous recovery In the majority of patients the disease runs its course over several years with eventual recovery Progressive functional impairment of a particular organ unfortunately is not rare however unrelenting disease terminating in death occurs only in a small percentage The prognosis for all forms of sarcoidosis as a whole therefore is good

The morbidity and mortality are largely dependent in the individual patient upon the degree of permanent functional damage to the particular organs involved Incapacitating permanent damage most commonly follows pulmonary and ocular functional impairment The mortality from all forms of sarcoidosis is probably less than 5 to 10 per cent Much higher mortality rates have been observed when the functional impairment involves such vital organs as the lungs and heart The cause of death is rarely attributable directly to sarcoidosis *per se* the most frequent immediate cause of death is cardiac failure secondary to changes induced by sarcoidosis in the lungs

Pulmonary tuberculosis once accounted for a significant percentage of the deaths in sarcoidosis The incidence of tuberculous infection has progressively declined and tuberculosis is now considered an infrequent although serious complication

Treatment Many approaches to therapy have been explored without discovery of a specific therapy for sarcoidosis Antimicrobial agents including isoniazid and streptomycin nitrogen mustards urethane tuberculin ultraviolet light heavy metals and many others are without significant therapeutic effect Roentgen therapy may be of benefit in certain superficial lesions Calciferol and dihydrotachysterol have been extensively investigated and some encouraging results in cutaneous lesions have been observed nevertheless intolerance and toxicity sharply limit their usefulness Splenectomy has been successful in correcting the thrombocytopenic purpura occasionally seen in sarcoidosis

Recent attention has been focused almost entirely upon the use of corticotropin and cortisone The active or proliferative stages of sarcoidosis show the most dramatic responses to corticotropin or the steroids The apparent improvement often is not maintained upon withdrawal of medication and relapses are the rule Favorable results have been most consistently achieved in ocular lesions of recent onset in particular uveitis There is little controversy about the indications for steroids to suppress lesions in vital tissues such as the central nervous system heart and kidney although the experience though encouraging is not yet sufficient to evaluate effectiveness The use of corticotropin or cortisone is controversial however in asymptomatic cutaneous lymphatic and osseous involvement the disadvantages of such therapy apparently outweigh its advantages in the majority of cases Acute manifestations such as diffuse pulmonary involvement with major difficulty in gas exchange have been temporarily suppressed in some instances by cortisone It is interesting that the evidence of functional change often does not correlate with the degree of subjective or roentgenographic improvement

It should be emphasized that the apparent beneficial effects induced by corticotropin cortisone or more recently prednisone and prednisolone have not been shown to alter the ultimate prognosis or mortality of the disease in the majority of patients with sarcoidosis The hazards of such therapy are certainly no less in sarcoidosis especially since the usual duration of therapy is from two to six months or it may be prolonged indefinitely The possibility of fulminating tuberculosis complicating adrenocorticosteroid therapy should be constantly in mind although the frequency of its occurrence has been relatively insignificant

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Prognosis The prognosis is usually favorable but occasionally a high fever dyspnea and rapid pulse develop followed by delirium and death

Treatment Treatment is symptomatic

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Miliary Fever

Definition Miliary fever is an acute infectious disease which occurs in epidemic form and is characterized by abrupt onset of fever excessive sweating prostration and erythematous rash

Incidence Most of the epidemics have occurred in Europe and the sweating sickness which swept over England during the fifteenth and sixteenth centuries was probably miliary fever An epidemic occurred in France in 1907 Zeiss made an epidemiological study of the disease in Russia in 1932 So far as is known the disease has never occurred in the United States

Etiology The cause of miliary fever is not known nor is its mode of transmission understood The epidemics which have been studied have occurred most frequently in the spring and summer months Persons of all ages are susceptible The mode of spread is rapid in this respect resembling that of epidemic influenza

Symptoms The most striking feature of miliary fever is the profuse perspiration It begins with the onset of fever which continues throughout the course of the disease The eruption which appears on the third or fourth day is usually of the papulovesicular type occurring first on the neck back and chest and later in the axillae and between the thighs Occasionally a purpuric form of the disease with other manifestations of hemorrhage is noted As the rash appears there is gradual diminution in the intensity of the symptoms and after two or three days desquamation occurs Convalescence is characterized by weakness loss of weight and slow recovery

Ainhum

(*Dactylolysis Spontanea*)

Definition Ainhum is a chronic disease of unknown cause usually affecting the little toe and characterized by the formation of a furrow at the digitoplantar fold which deepens and extends until the toe is encircled and eventually separated from the foot

Incidence Ainhum has been observed chiefly on the west coast of Africa and in Brazil Cases have been reported also from the West Indies Panama and rarely from the southern part of the United States Apparently white people are not susceptible nearly all the cases reported have been observed among nonwhites There is some evidence that ainhum is a familial disease since it may occur in several members of the same family or in repeated generations of the same family It occurs chiefly in male adults between twenty five and thirty years of age

Etiology There have been various theories as to etiology Some have claimed that ainhum was related to leprosy This seems however most unlikely it is much more probable that the disease is a trophoneurosis secondary to some local trauma Chancey and Gipson look upon ainhum as a symptom not a primary disease and believe that it may occur in many conditions Kean and Tucker reviewed 45 cases from the Isthmus of Panama in 1946 and concluded that the cause of ainhum is still unknown and its pathogenesis not clear

Morbid Anatomy In a typical case a fibrous cord replaces the bony structures

normally attaching the bone to the foot The skin becomes thickened and the walls of the blood vessels show an endarteritis with a secondary rarefying osteitis

Symptoms According to Still the little toe is the one affected in 90 per cent of the cases more rarely the fourth toe and very rarely both the fourth and the little toe are involved Both little toes may be attacked at the same time but the condition usually starts in one toe The initial appearance is featured by a crack in the digitoplantar fold of the little toe This extends laterally and finally appears on the dorsum of the toe The distal portion of the toe enlarges and becomes bulbous In the final stages the connection between the foot and the little toe is a slender fibrous cord which permits the toe to wobble in various directions and to interfere greatly with walking

The course of the disease extends over several years if the toe does not undergo spontaneous amputation as a result of injury to the pedicle The disease is practically painless

Treatment Ainhum is best treated in the early stages by longitudinal incision into the grooved furrow In the later stages amputation is usually necessary

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Milk Sickness

(Trembles)

Milk sickness better known as the trembles is an afebrile disease due to the ingestion of milk milk products or the flesh of animals suffering from the disease

Milk sickness is now more or less a medical curiosity but in the first half of the nineteenth century it constituted a major problem on the western frontier of the United States

History Nicolay and Hay in their "History of Abraham Lincoln" claim that Nancy Hanks the mother of Lincoln died of milk sickness In the autumn of 1818 the little community of Pigeon Creek was almost exterminated by a frightful pestilence called the milk sickness " Nancy Hanks was one of the victims

Incidence At the present time milk sickness is a rare disease but a century ago the condition was common in various parts of the United States It was quite prevalent throughout the Mississippi Valley particularly in Ohio Indiana Illinois and Michigan There is no record of milk sickness ever having occurred outside the United States

Etiology The evidence seems to be fairly conclusive that milk sickness is caused in the majority of cases by a plant known as white snakeroot *Eupatorium urticaefolium* In New Mexico and Arizona this plant has not been observed but what is apparently the same disease also occurs in these states and is due to another herb the rayless goldenrod *Aplopappus heterophyllus* which probably contains the same toxic agent found in white snakeroot In man the disease results from eating butter or drinking the milk from cattle which have ingested the weed It is also possible for the human being to be poisoned by the beef of cattle that have eaten of this plant When extract of white snakeroot is fed to laboratory animals they become ill refuse food and develop a generalized tremor Couch who was one of the first to isolate a toxin from white snakeroot named it *trematol* which according to Couch exists in the plant partly in ester combination with a resinous acid

Symptoms Milk sickness is characterized by a gradual onset of weakness loss of appetite and vomiting These early symptoms are followed by constipation and abdominal distress There is no fever but marked thirst is usually noted The mind is clear but in fatal cases coma may precede death by several hours The average duration of the disease is seven to nine days although symptoms may continue much longer

Prognosis The prognosis is grave in both acute and subacute cases Moseley states that the death rate is about 25 per cent

Treatment The treatment is purely symptomatic Prophylaxis consists of avoiding meat and milk products of animals with trembles and in pasturing cattle on cleared or plowed land

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Diseases of Allergy

Introduction

RELATION OF ANTIGEN ANTIBODY REACTIONS TO ALLERGIC DISEASES

The clinical manifestations of allergic reactions result from the combination of an antigen with an antibody which has been formed by the host generally in response to prior contact with the antigen Hay fever asthma food and drug allergy and allergic dermatitis usually are caused by noninfectious antigens of environmental or extrinsic origin However the pathological changes of chronic infection often may be caused in large part by an allergic response of the host to the invading microorganism Furthermore the morphological and physiological changes which characterize such diseases as periarteritis nodosa lupus erythematosus rheumatoid arthritis glomerulonephritis rheumatic fever and encephalomyelitis are thought by some to result from autoantibody production to antigens present in the individual s own tissues In chronic thyroiditis Hashimoto s disease precipitating antibodies to human thyroglobulin have been found and an analogous pathological process has been produced by injecting rabbit thyroid into rabbits In erythroblastosis fetalis antibodies derived from the mother pass through the placenta to combine with antigens on the erythrocytes of the fetus The degeneration of homologous skin and other tissue grafts may be also attributed to the formation by the recipient of antibodies to the grafted tissues Recent studies with inbred strains of mice have shown that injection of spleen cells or whole blood into fetuses *in utero* endows them with the ability to tolerate skin grafts from donor strains which would ordinarily be rejected this has been termed *actively acquired tolerance* (Medawar) Destruction of the graft could be effected by transplantation of a lymph node from an animal which had previously rejected a graft From the immunological standpoint therefore allergy is an ever broadening field with a profoundly important relation to pathology and clinical medicine

Allergic reactions to extrinsic antigens may be separated broadly into two groups One of these is associated with the presence of circulating antibody in the serum of affected individuals and includes anaphylaxis Arthus reactions serum sickness allergies involving the characteristic wheal and erythema reaction hay fever urticarias angioedema asthma and certain gastrointestinal allergies In the other an antibody having a high affinity for tissue cells has been demonstrated and circulating antibody is thought not to be involved This latter group includes contact dermatitis (*e g* poison ivy sensitivity) drug allergies (sulfonamides penicillin) and certain allergies of infection The allergic reactions observed in these two groups are frequently referred to as immediate and delayed respectively These terms are sometimes useful in distinguishing anaphylaxis and urticarial reactions from contact dermatitis and tuberculin sensitivity but are ambiguous as applied to the Arthus and tuberculin reactions as well as drug sensitivities in which microscopic evidence of reaction occurs early but in which several hours are required before they become visible grossly

Since allergic diseases are a manifestation of the response of tissues to an antigen antibody reaction an understanding of their mechanism depends largely upon a knowledge of the seven aspects to be considered in detail subsequently None of these problems have been completely solved but a substantial body of information has

been accumulated from studies on human allergy and from animal experimentation

1 The Nature of the Inciting Antigen(s) Proteins and polysaccharides are capable of stimulating antibody formation in animals and in man and these comprise most of the allergenic substances Both are widely distributed throughout the animal and plant world and almost any protein constituent (and some polypeptides) can under suitable *experimental circumstances* be shown to elicit an antibody response In sensitivities caused by low molecular weight substances such as common drugs it is generally believed from the work of Landsteiner and co workers that these substances *are in some way coupled to* protein in the animal and in this way induce the formation of antibody Sensitization is more easily accomplished in animals and man with low molecular weight substances which combine readily with protein than with less highly reactive substances To be antigenic proteins must be foreign to the circulation of the host *e g* antibodies are not produced by the injection of human serum proteins from man to man In hemolytic anemias the production of auto antibodies to erythrocyte antigens may occur but the mechanism of this sensitization is unknown a recent case was shown to be due to production of antibodies to one of the rare Rh factors e or Hr' by a *person whose erythrocytes contained this* antigen

Purified polysaccharides are antigenic in certain species but not in others The type specific pneumococcal polysaccharides and dextrans for example are antigenic in man and give rise on injection to precipitins and to wheal and erythema sensitivity Antibodies and skin sensitivity to certain polysaccharides occur in a considerable proportion of humans sensitization probably resulting from microorganisms in the nasopharynx and the gastrointestinal tract which produce these polysaccharides Indeed the infusion of certain dextrans into such sensitized persons has produced urticarial and other anaphylactic symptoms In other species such as the rabbit and guinea pig these polysaccharides are antigenic only when combined with protein or in the intact microorganism High molecular weight preparations of the completely synthetic polyvinylpyrollidone have been shown to be antigenic in humans Gelatin long thought not to be an antigen has also been shown by Maurer to be antigenic in several species

In experimental animals using well defined or purified proteins the sensitivities produced are most frequently associated with circulating antibody and are similar to the allergies encountered in the administration of foreign proteins (*e g* horse antitoxins) to man as typified by serum sickness and anaphylactic reactions The high proportion of allergic sensitizations affected by contact with such foreign proteins in man necessitates the use of a preliminary *intracutaneous test prior to parenteral* administration of even small amounts of an antitoxin or other foreign protein This may be performed with about 0 01 to 0 02 ml of 1 10 diluted serum a positive wheal and erythema reaction after about 20 minutes *indicates sensitivity*

Delayed type allergic reactions are less amenable to study since they are generally the result of infections with intact microorganisms which are extremely complex mixtures of antigens (*e g* tuberculin mallein) and thus are far more complicated from the immunological standpoint Drug sensitivities and poison ivy sensitivity are also of this delayed type the experimental production of drug sensitivities in animals provides instances of less complicated antigenic systems

The factors determining whether a substance will be antigenic and whether allergic sensitization will or will not be associated with circulating antibody are *completely obscure and our present* knowledge is entirely empiric

2 Ways in Which Sensitization Can Take Place Sensitization to various antigens may occur following introduction of antigen by parenteral respiratory oral or other routes In experimental animals and man *sensitization* to serum proteins of another species can be induced in almost all instances Serum sickness has occurred in over 90 per cent of persons treated with large amounts of horse antipneumococcal serum Similarly the development of skin sensitivity to tuberculin may be produced in tuberculin negative persons by vaccination with BCG On the other hand only a relatively small proportion of the population develop the usual allergic diseases produced by grass and tree pollens *danders* and certain foods Efforts to induce skin sensitivity hay fever asthma or other manifestations of allergy with these antigens in man have been generally unsuccessful although anaphylactic sensitivity may be produced in guinea pigs fairly readily Naturally occurring human allergies are sometimes termed spontaneous allergies to distinguish them from induced allergies

3 Predisposing or Hereditary Factors Studies in various experimental animals have shown that by inbreeding and selection it is possible to establish strains differing widely in susceptibility to certain bacterial infections capacity to produce antibody and ability to become sensitized to certain simple chemical compounds Such data indicate that heredity influences these phenomena Evidence that similar genetic factors affect the development of the spontaneously occurring allergies in man is far more difficult to obtain Suggestions that these allergies are inherited on a Mendelian basis have been based on the occurrence of families with a large proportion of allergic members Critical re examination of such family studies established that in about 40 per cent of the families only a single individual was allergic and that in an additional 25 per cent only one other member had allergy only a small fraction of the families had many allergic members With only such data the existence of genetic determinants in these human allergies must be considered as unproved

4 Properties of the Antibodies Involved A number of antibodies have been recognized in both experimental animals and man which differ in their capacities to induce allergic sensitivities These antibodies may vary in their ability to react with antigen to sensitize a heterologous species passively to elicit a wheal and erythema reaction or in their affinity for tissue cells To a limited extent certain of these properties have been related to certain types of allergic response

The usual type of precipitin produced after the injection into a rabbit of a foreign protein such as egg albumin can passively sensitize the guinea pig or rabbit for anaphylactic shock or the Arthus reaction However the antibodies produced by the rabbit to such an antigen are not all identical but are thought to represent a spectrum of antibodies differing in reactivity Certain of the antibody molecules in such an antiserum do not by themselves precipitate with antigen They precipitate with other antibody molecules if sufficient antigen is added at one time but remain in the supernatant serum if precipitation is carried out fractionally by successive serial addition of small amounts of antigen This type of antibody is termed nonprecipitable since it cannot precipitate with antigen by itself but can only attach itself to a specific precipitate formed in the presence of precipitable antibody Precipitable and nonprecipitable rabbit antibodies to egg albumin have been shown to be equally effective in inducing passive anaphylactic sensitization in the guinea pig the nonprecipitable antibody however was incapable of inducing an Arthus type of sensitization passively Conversely certain types of horse antibody such as horse antibody to the pneumococcal polysaccharides are for unknown reasons incapable of inducing passive anaphylactic sensitization of the guinea pig However they precipitate with the pneumococcal polysaccharides and have been shown to induce a passive Arthus reaction in the guinea pig From this and other evidence the Arthus reaction may best be interpreted as due to mechanical damage to blood vessels resulting from precipitation of antigen and antibody while anaphylaxis is a consequence of the combination of antigen with antibody and is largely independent of precipitation Some individuals have been shown to produce a nonprecipitating variety of diphtheria antitoxin which was also capable of passive anaphylactic sensitization of the guinea pig Precipitating antibodies have been found in humans who have developed serum sickness Since horse serum is a complex mixture of antigens the relation of the clinical manifestations to the disappearance of antigen and the appearance of antibody is difficult to determine However in studying serum sickness following the administration of crystalline bovine albumin Kendall was able to demonstrate that the clinical manifestations coincided with accelerated disappearance of antigen from the circulation and that circulating antibody appeared shortly after symptoms subsided

It is of importance to remember that persons who have experienced serum sickness or formed antibody to such foreign protein may be thrown into anaphylactic shock Furthermore lesions wholly similar to those of periarteritis nodosa have been found in animals and in man following administration of large amounts of foreign serum Rare instances have also been recorded in which an acute demyelinating disseminated encephalomyelitis followed the administration of pertussis vaccine

The spontaneous allergies of the wheal and erythema type have been shown frequently to be associated with antibody in the circulating blood The antigen or antigens responsible for such sensitivity may be identified by skin testing with a variety of extracts from trees grasses and pollens Because of the danger of inducing severe systemic reactions minute doses of such

extracts are employed Extracts are standardized on the basis of their protein nitrogen content and their potency is frequently expressed in units one unit is 0 01 microgram protein nitrogen Two techniques are generally used—the scratch test and the intracutaneous test The former is considered to be somewhat safer but the latter is more sensitive Skin tests are generally performed on the arm or forearm a location which offers the opportunity for controlling development of any systemic reaction from the test by application of a tourniquet The scratch test is usually performed by making a small scratch with a hypodermic needle gently rubbing a drop of the allergenic substance into the skin over the scratch The intracutaneous test is carried out by the injection into the most superficial layers of the skin of about 0 01 ml of the allergen solution this quantity is usually the minimal amount producing a detectable bleb Control tests with diluent alone are always carried out The appearance after fifteen to thirty minutes of a wheal with surrounding erythema which is absent in the control is taken as a positive test In carrying out such tests it is essential to start with extremely dilute solutions (10 to 100 units per ml) to avoid severe constitutional reactions If negative results are obtained further tests may be made with increasing concentrations usually tenfold increments

Antibodies in the serum of persons showing such skin sensitivity may be identified by passive transfer of such serum into the skin of nonsensitive persons (Prausnitz Kustner reaction) After six hours to five or ten or even more days antigen is injected into the same site and the occurrence of a wheal and erythema reaction are noted

While allergic persons generally show skin sensitivity of the wheal and erythema type to one or more of the offending antigens it is not uncommon to find skin sensitivity in those who do not show clinical manifestations of disease on exposure to this allergen A substantial proportion of persons with skin sensitivity to a given antigen have antibodies in their serum capable of giving a Prausnitz Kustner reaction Despite extensive study no unequivocal *in vitro* manifestation of the presence of these skin sensitizing antibodies has been demonstrated Recent attempts to associate them with a nonprecipitating antibody are open to considerable question in view of the failure to employ serum shown to be free from precipitating antibodies to other antigenic impurities

Another type of antibody in human serum to antigens associated with the wheal and erythema types of allergy has been demonstrated by Cooke and coworkers by Harley and subsequently by others This antibody is formed in response to the parenteral injection of antigen It may be formed in sensitive individuals receiving injections of antigens such as ragweed extracts for therapeutic purposes and is also formed when nonallergic individuals receive similar injections These antibodies do not sensitize human skin but combine with their homologous antigen so that the antigen cannot react with the skin sensitizing antibody to give a wheal and erythema response These antibodies which have been termed *blocking antibodies* differ in several respects from skin sensitizing antibodies They are stable to heating at 56° C for four hours a procedure which destroys the activity of the skin sensitizing antibody Unlike the skin sensitizing antibody they diffuse away from the site of injection and also are able to pass the placenta Finally recent studies have shown that serums with high titers of blocking antibody to ragweed extract not only combine with antigen to prevent a skin reaction but can also bind antigen so that the antigen is unable to combine and fix complement with rabbit antibody to ragweed extracts this latter capacity is measured by a complement fixation inhibition or indirect complement fixation test The blocking antibody will also agglutinate tannic acid treated erythrocytes coated with antigen and can inhibit precipitation of rabbit antiragweed serum by ragweed extracts Blocking antibody may eventually be shown to be a classic type of precipitating antibody if obtainable in adequate quantities The major unsolved problems in wheal and erythema allergy are the nature of the skin sensitizing antibody the manner in which it is produced how it is able to attach itself to skin and whether or not it would behave as a precipitating antibody if obtained in sufficient quantities

The antibody associated with allergies of the delayed type appears to be different from these other antibodies People and animals showing delayed or tuberculin type sensitivities do not appear to have antibodies which can passively transfer this type of sensitivity in their serum Studies of Landsteiner and Chase however have shown that skin sensitivity of the delayed

type in guinea pigs may be transferred passively to nonsensitive animals of the same species by the administration of cell exudates With larger amounts of washed cell exudates Chase has also been able to transfer anaphylactic sensitivity and antitoxic immunity Studies in man have also successfully demonstrated passive transfer of sensitivity to tuberculin by injecting leukocytes from tuberculin positive into tuberculin negative subjects lysed cells have been found to be capable of effecting this transfer The sensitivity does not make its appearance for two to three days after the cells are introduced The mechanism of transfer of delayed sensitivity has not yet been clearly defined

5 **Quantitative Relationships between Antibody and Antigen and the Allergic Responses** An important consideration in the understanding of the mechanisms of allergy is a knowledge of the amounts of antibody required to bring about allergic reactions Passive sensitization may be effected by injecting measured volumes of rabbit or guinea pig antiserum to purified antigens of known antibody content into guinea pigs and then after a suitable interval injecting antigen With this technique it has been shown that only 30 micrograms of rabbit or guinea pig antibody nitrogen need be present in a 250 gm guinea pig for uniformly fatal anaphylactic shock to occur with human diphtheria antitoxin about 100 micrograms was needed Uterine strips from a guinea pig passively sensitized to egg albumin might be expected to contain about 0 01 microgram of antibody N such uterine strips show maximal contraction when exposed to antigen in a Dale bath Ovary has shown that injection into guinea pig skin of but 0 003 microgram of antibody N was sufficient to cause a wheal and erythema type of reaction on contact with antigen This reaction called passive cutaneous anaphylaxis is readily demonstrated by intravenous injection of antigen mixed with a dye such as Evans blue the skin sites at which the antibody was placed become blue owing to increased permeability into the wheal The latent period in passive anaphylaxis *e g* the time interval between the sensitizing dose of antibody and the shocking dose of antigen has been shown both in systemic anaphylaxis and with isolated uterine strips to be a function of the quantity of antibody used for sensitization with large amounts of antibody N fatal anaphylaxis could be obtained with no latent period but as the quantity of antibody N used for sensitization decreased the latent period increased Passive cutaneous anaphylaxis in guinea pigs can be produced only with serum from humans with induced allergies and not from those with spontaneous allergies

The passive Arthus reaction requires far larger quantities of antibody N To produce a minimal Arthus reaction 25 micrograms of antibody N in the rabbit and about 10 micrograms in the guinea pig must be injected into a skin site These quantities of antibody are of the order of 1000 to 2500 times larger than that estimated to be present in a contracting uterine strip or 3000 to 10 000 times greater than that responsible for passive cutaneous anaphylaxis in guinea pig skin

The very minute amounts of antibody required to elicit wheal and erythema and anaphylactic reactions suggest the possibility that the failure to detect *in vitro* manifestations of skin sensitizing and blocking antibodies may be due to the small quantities involved it cannot be excluded however that certain of these antibodies may possibly prove to be of the nonprecipitable variety which as described above can produce anaphylactic sensitivity

6 **The Mechanisms by Which Combination of Antigen and Antibody Causes an Allergic Response** A number of the physiological and pathological manifestations of immediate type anaphylactic reactions notably the patterns in anaphylactic shock the wheal and erythema reaction in human skin and the contraction of smooth muscle may be produced by the injection of histamine and these findings have led to the belief that the antigen antibody combination liberates histamine Further evidence rests on the similarity of the effects produced in various species by certain diamines and mono- or diamidines a group of substances termed histamine liberators For instance if a sensitized guinea pig which has also received an injection of pontamine sky blue is thrown into anaphylactic shock the localization of the blue dye in certain characteristic areas is very similar to that produced in a guinea pig injected with a histamine liberator Furthermore the areas of skin selectively colored by the blue dye in both instances are those which contain the highest concentrations of histamine

Anaphylactic shock and the effects of histamine itself or of histamine liberators in the guinea pig may be prevented by the antihistamine drugs

However other species notably the mouse are extraordinarily refractory to

histamine and in these species 5 hydroxy tryptamine (serotonin) may play the dominant role in anaphylaxis lysergic acid diethylamide and reserpine inhibit anaphylactic contraction in the sensitized mouse uterus while antihistaminics are ineffective Humans with malignant carcinoid show a peculiar type of bronchial asthma and patchy flushing of the skin similar effects can be produced with 5 hydroxytryptamine Carcinoid tissue contains much 5 hydroxytryptamine and these patients have high blood serotonin

Evidence for yet another substance slow reacting substance (SRS) has been obtained with sensitized guinea pig and human asthmatic lung tissue When the effects of histamine are counteracted by the antihistamines a substance is released on contact with antigen which causes a slow sustained contraction of guinea pig ileum it is distinct from other substances known to affect smooth muscle

Little is known of the mechanisms by which antigen antibody combination brings about other allergic manifestations

7 Factors Affecting Antibody Formation and the Allergic Response Roentgen irradiation has been shown to reduce or inhibit antibody formation if administered prior to the injection of antigen Several substances notably the nitrogen mustards corticotropin and cortisone have also been shown to suppress but not completely abolish antibody formation and to have a suppressive effect on the specific anamnestic response As a consequence in actively sensitized animals receiving these drugs the Arthus reaction which requires fairly substantial antibody levels has been reduced in severity However anaphylactic reactions in actively sensitized animals which require relatively minute quantities of antibody are not affected by these substances Cortisone and corticotropin have been shown not to influence the combination of preformed antigen and antibody in that both passive anaphylaxis and the passive Arthus reaction are unaffected Cortisone has been found useful in the treatment of certain allergies notably serum sickness hay fever asthma contact dermatitis infantile eczema and drug allergies and less effective in urticarias and angioedema in large doses it also reduces the intensity of the tuberculin reaction These actions may also result from an effect on inflammation rather than from suppression of antibody formation since the cortisone frequently acts much more rapidly than inhibition of antibody synthesis would be expected

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Hay Fever

Definition *Allergic rhinitis* is a reaction of the nasal mucosa manifested by edema itching and increased mucous secretion and is the result of allergy to a specific antigen When caused by allergy to pollens it is called *hay fever* or pollenosis and is characterized by seasonal recurrence during the period of pollination of the causative plants Allergic rhinitis due to antigens other than pollens is called *nonseasonal* or *perennial allergic rhinitis* The term *vasomotor rhinitis* is applied both to perennial allergic rhinitis and to morphologically similar chronic edema of the nasal mucosa due to nonantigenic irritants or probably in some cases to neurogenic and psychosomatic causes

Etiology The occurrence of symptoms of hay fever depends upon the development of allergy of the wheal and erythema type" for pollen and subsequent inhalation of the specific pollen in adequate quantity to elicit the allergic reaction The allergic sensitization producing hay fever is the

same type associated with infantile eczema atopic dermatitis bronchial asthma and certain forms of food allergy so that persons manifesting one of these diseases frequently develop others of the group While diseases of this group tend to occur in certain families neither the particular disease manifestation nor allergy to a specific antigen is inherited only a tendency to become allergic to antigens to which the individual is exposed

In general only those plants depending on the wind for cross pollination and producing an abundance of buoyant windborne pollen are important factors in the causation of hay fever These include grasses many families of weeds and most of the trees of temperate climates Plants with showy and odoriferous blossoms including roses and goldenrod which are adapted to insect pollination and produce relatively small amounts of heavy sticky pollen rarely cause hay fever Allergy to tree and weed pollens is specific for the genus rather than the species of plant so that the use of pollen of one species of a genus in testing and treatment suffices In the case of the grasses the pollens of all the common genera are antigenically quite similar so that for practical purposes a mixture of the pollens of three or four of the grasses most common in a given area may be used as if a single antigen

Specific diagnosis of hay fever requires a knowledge of the flora of the patient s locality and the seasons of pollination of the plants Throughout the greater portion of the United States and southern Canada spring hay fever (April and May) is due to tree pollens early summer hay fever (June and July) to grass pollens with plantain and sorrel also important in some areas and late hay fever (August and September) to weed pollens The important trees vary considerably in different areas ash beech birch cedar hickory maple oak sycamore and poplar produce an abundance of antigenic windborne pollen and may be presumed important where they grow commonly The pollens of the pines and other conifers are relatively less antigenic and less often cause hay fever even where abundant The grass pollens are everywhere important their season being prolonged through much of the year in the extreme south In the East and Middle West ragweed is by far the most important weed pollen it also occurs in most of the Far West except for the North Pacific coast but its importance in the mountain and coast areas is less than that of sage amaranth and Russian thistle For detailed accounts of the windborne pollens causing hay fever in various areas of the United States and southern Canada reference to the works of Wodehouse and of Durham is suggested The tree and grass hay fever seasons in northern Europe correspond closely to those of the United States the weed pollens are relatively much less important ragweed not being indigenous to the area

Incidence It has been estimated that 8 to 10 per cent of the population of the United States is affected by hay fever but a large proportion of these cases are not severe enough to require medical treatment The white Negro and yellow races are susceptible Both sexes are equally affected In areas where ragweed is abundant approximately 75 per cent of hay fever sufferers are affected by this pollen in 50 per cent it is the only significant cause About 50 per cent are affected by grass pollens alone or in combination with other pollens Tree hay fever is less common and usually occurs in patients also affected by grass or weed pollens

Pathology and Physiology Since one of the chief functions of the nose is to warm and purify the inhaled air a large proportion of suspended dust particles are deposited on its mucosa which is therefore peculiarly exposed to inhaled allergens Sensitization of the type causing hay fever consists in the development of sensitizing antibodies present in the conjunctiva nasal mucosa skin and blood plasma Contact of the allergenic pollen with the sensitized mucosa elicits an antigen antibody reaction which is manifested by engorgement of the blood vessels edema increased secretion of watery mucus and itching which gives rise to sneezing The physiological effects of the antigen antibody reaction are believed to result from the release of histamine which can be demonstrated when specific antigen is added to the patient s blood *in vitro* There is little evidence that the central nervous system is involved

While the symptoms produced by inhalation of pollen are localized to the mucosae with which it comes in contact the sensitization is systemic Injection of too large a quantity of antigen into a highly allergic patient in a diagnostic skin test or in treatment may elicit a *constitutional reaction* similar to experimental anaphylactic shock It is manifested within twenty minutes or less by coughing sneezing asthma urticaria or general flushing and itching of

the skin and in severe cases collapse Such reactions may be serious or even fatal if not promptly treated

Repeated injections of the antigen for the specific treatment of hay fever stimulate the formation of blocking antibody distinct from the pre existing sensitizing antibody This blocking antibody appears to be responsible for the increase of tolerance for injected antigen and may be responsible for the clinical benefits of treatment although evidence of the latter is still inconclusive

Symptoms The symptoms of hay fever characteristically recur each year at the same season with the beginning of pollination of the causative plant the date of onset in a given locality rarely varying by more than a week or so although the amount of pollen produced and hence the severity of symptoms vary considerably from year to year depending on the weather During the season symptoms are worse on dry windy days and decrease during heavy rain They usually tend to be worse in the morning The termination of symptoms at the end of the pollen season is less abrupt than the onset owing to the persistence of pollen in the air and in many cases to the complicating effects of nonseasonal allergens and superimposed respiratory infections

The most characteristic symptom is sneezing usually in paroxysms of several sneezes in rapid succession The nasal mucosa is congested and there is an increased flow of watery mucoid secretion The conjunctivas are red and itchy with increased lacrimation Itching of the soft palate and pharynx is usual and in severe cases the ears may also itch severely Cough wheezing and dyspnea are commonly present but are actually indicative of pollen asthma rather than hay fever itself

Diagnosis When the pattern of seasonal recurrence has become established the diagnosis of hay fever is easy and the causative pollen is usually apparent to the physician acquainted with the pollen seasons of the area During the first season differentiation from infective rhinitis may be difficult although the paroxysmal sneezing the itching of the eyes and pharynx the watery nasal discharge the normal temperature the absence of sore throat and of general malaise are helpful as is a personal or family history of allergies of the wheal and erythema type In doubtful cases smears of the nasal secretion may be stained with Wright s stain an abundance of eosinophils is characteristic of allergic rhinitis

Allergic rhinitis due to antigens other than pollens particularly airborne molds such as Alternaria and Hormodendrum and seasonal insects may have a seasonal exacerbation during warm weather but lacks the precise onset and cessation characteristic of pollen allergy Occasional cases of allergic rhinitis due to fruits or vegetables eaten at certain seasons may be confusing but can be distinguished by skin tests

The diagnosis of hay fever is established and the specific cause demonstrated by eliciting the wheal and erythema reaction in skin tests with the antigen performed with the technique and precautions outlined in the introductory section on allergy Both the *scratch test* and the *intracutaneous test* are useful the former is simpler and involves less danger of a general constitutional reaction the latter is more sensitive and more useful in estimating the degree of sensitization For the typical case of seasonal hay fever a few tests with pollens appropriate to the season and locality suffice If the season is prolonged additional tests with mold spores and other inhalants may be added (See section on Nonseasonal Allergic Rhinitis)

Reactions are read after ten to fifteen minutes A slight but definite wheal is considered one plus a moderate reaction (wheal 6 to 10 mm without pseudopods) two plus a wheal of 10 to 15 mm (with pseudopod formation) marked or three plus and wheals larger than 15 mm four plus

The initial intracutaneous tests with pollens should be made with solutions of antigen containing no more than 10 protein nitrogen units per ml and not more than six tests should be done at one time If little or no reaction is obtained subsequent tests may be made with solutions containing 100 units and then 1000 units per ml until a two or three plus reaction is elicited

The degree of sensitivity is roughly indicated by the highest dilution producing a marked (three plus) skin reaction in the intracutaneous test Class A highly sensitive 10 units per ml Class B average 100 units and Class C less sensitive 1000 units A moderate (two plus) reaction to the 1000 unit strength is evidence of sensitivity if consistent with the seasonal incidence of symptoms Many patients with definite allergy to one pollen show slight or moderate reactions to many other pollens These indicate slight or potential

allergy but specific treatment is indicated only for those which the history shows to be important

Prognosis Hay fever is essentially a permanent idiosyncrasy more troublesome than disabling and without danger to life Variations in severity may occur spontaneously or as a result of a change of residence or habits which alters the intensity of exposure to pollen Since hay fever is a manifestation of allergy of the wheal and erythema type patients affected by it often develop other diseases of this type particularly asthma This complication eventually occurs in approximately 30 per cent of untreated patients but the incidence is greatly reduced by specific treatment Patients with hay fever are unusually susceptible to upper respiratory infection and the development of sinusitis is a common complication especially of the fall type which persists until the cold weather when respiratory infections are prevalent

Treatment The treatment of hay fever consists of (1) avoidance of the causative pollen (2) palliative drug therapy (3) lessening of sensitivity by injections of the specific antigen When treatment is started during the season of symptoms the first two methods produce the most immediate relief but the most satisfactory results over the long term are achieved by antigen injections started at least two months before the season

Avoidance When the severity of symptoms warrants it relief may be obtained by a trip to an area known to be free of the causative pollen or by a sea voyage Exposure to pollen may also be lessened by air conditioning or the use of suitable pollen filters in the window of the bedroom or other rooms to a lesser degree by simply remaining indoors with windows and doors closed

Palliative Treatment The most useful drugs are the antihistaminics which produce satisfactory relief in a majority of cases Tripelennamine (Pyribenzamine) 50 mg chlorprophenpyridamine (Chlor trimeton) 4 mg and chlorcyclizine (Perazil or Di Paralene) 25 mg are examples of the many suitable drugs of the group They may be taken after each meal and if necessary every four hours at night Phenergan (12 5 to 25 mg) has a more potent and lasting antihistaminic action and is useful at bedtime but is too sedative for general use during the day

Patients with severe symptoms or with coexisting pollen asthma not relieved by the antihistaminics may be given prednisone or prednisolone 5 mg every six to eight hours or corticotropin gel 40 units intramuscularly daily The dose of either drug should be reduced by 25 to 50 per cent as soon as relief is obtained and is generally continued only for seven to ten days at the height of the pollen season

For relief of the conjunctival symptoms eye drops containing cocaine hydrochloride 0 3 per cent epinephrine hydrochloride 0 025 per cent and boric acid 3 per cent in rose water are useful one drop in each eye two or three times a day if necessary

Specific Treatment Treatment with specific pollen antigen consists of a series of twelve to sixteen subcutaneous injections of gradually increasing doses of antigen given at intervals of three to seven days starting two or three months before the season The following table shows approximate doses which must be modified according to the patient s reaction

Dosage in Protein Nitrogen Units for Treatment of Hay Fever

DOSE	CLASS A (HIGHLY SENSITIVE)	CLASS B (AVERAGE CASE)	CLASS C (LESS SENSITIVE)
1	2	10	20
2	5	20	40
3	10	40	80
4	20	80	150
5	35	140	250
6	50	200	400
7	75	300	600
8	110	400	850
9	150	600	1200
10	200	800	1800
11	300	1000	2500
12	400	1500	3500
13	600	2000	5000
14	800	3000	6500
15	1000	4000	8000
16	1000	5000	10000

The injections are given on the lateral aspect of the upper arm or the thigh with a rubber tourniquet and epinephrine 1 1000 at hand for use in case of a constitutional reaction The patient is kept under observation for twenty minutes after the injection

Normally the injections produce a slight local swelling which subsides within twenty four hours If the local reaction is troublesome or lasts longer than thirty six hours the same dose is repeated after the usual interval then increased or again repeated as indicated by the resulting reaction

If a constitutional reaction follows the

injection a rubber tourniquet is applied promptly proximal to the site of the injection and epinephrine 1 1000 0 4 to 0 6 ml injected every ten minutes until relief is obtained Mild constitutional reactions may be relieved by tripelennamine (Pyribenzamine) 50 to 100 mg orally or 25 mg subcutaneously but since they may rapidly become more serious the inexperienced physician is wise to use epinephrine When a constitutional reaction has occurred the dosage should be dropped back two steps on the schedule and then increased more gradually If a second constitutional reaction occurs at the same dosage the subsequent dosage should be kept below that level

The dose which has been reached at the beginning of the season is repeated weekly during the period of active pollination without further increase

Suitable injection treatment produces satisfactory results in at least 75 per cent of cases but may be supplemented with drug treatment if necessary If the results of injection treatment are not satisfactory and no undue reactions have occurred the following season one may plan to reach a dose two or three times as great

If treatment is to be repeated the following year more satisfactory results may be expected with no greater total number of injections by the perennial method of treatment After the end of the season the same dose is repeated every four weeks until the following spring When a fresh supply of extract is obtained the dose must be reduced 50 to 60 per cent to allow for the deterioration of the year old antigen it can then be gradually increased to the previous or a somewhat higher dose by giving injections every two weeks

If injections of antigen have not been given before onset of symptoms attempts to start specific treatment during the season are rarely effective and palliative treatment is more satisfactory

NONSEASONAL ALLERGIC RHINITIS VASOMOTOR RHINITIS

Allergic rhinitis due to nonseasonal antigens is essentially similar to hay fever and often affects the same persons but if exposure to the antigen is persistent it assumes a chronic form Perennial allergic rhinitis may be due to inhaled antigens (inhalants) or to allergic reactions to the bacteria of the nose and paranasal sinuses and rarely to foods or ingested drugs Ordinary house dust contains antigens distinct from the known substances contributing to its formation but possibly resulting from their deterioration and is one of the most important inhalant antigens

Vasomotor rhinitis practically indistinguishable from chronic allergic rhinitis may result from prolonged exposure to nonantigenic irritants of which the most frequently encountered are vasoconstricting nose drops such as ephedrine Privine and Neo Synephrine When these drugs have been used persistently they frequently prove to be the principal cause of prolonged rhinitis and marked improvement results within a week after their discontinuation A similar edema of the nasal mucosa can also result from psychosomatic factors which may occasionally be the sole cause but more often are a contributory cause in allergic cases

In rhinitis due to any of these causes the nasal mucosa is markedly swollen and presents a dull red or grayish appearance In chronic cases there are often mucous polyps particularly in the ethmoid region The nasal secretion is increased in amount and mucoid in character with an abundance of eosinophils in the stained smear

To evaluate the importance of extrinsic allergens skin tests with eighteen or twenty of the principal inhalants should be done as outlined in the section on asthma Tests with food antigens are indicated only if the history is suggestive or if the inhalant tests give negative results Skin tests are not satisfactory for determining the existence of bacterial allergy in the causation of vasomotor rhinitis It may be suspected in the presence of associated chronic sinusitis particularly hyperplastic sinusitis and is strongly suggested by the coexistence of nasal polyps If the patient has been using vasoconstricting nose drops persistently their use should be discontinued before the importance of other factors is estimated The importance of psychogenic factors in certain cases of vasomotor rhinitis either as the principal cause or as a contributory factor in allergic patients must be judged by the history by the careful elimination of allergic and infective causes and by observation over a period of time

Treatment is best directed to the cause In cases due to specific inhalant antigens such as feathers or animal danders elimination of contact is far more effective than injection treatment Allergy to inhalants with which contact is unavoidable such as house dust and airborne mold spores is treated by injection of antigens in progressive dosage similar to that advised for

pollen antigens For symptomatic treatment the antihistaminic drugs in the doses advised for hay fever are useful but are somewhat less effective in chronic than in acute cases Prednisone prednisolone and corticotropin are highly effective in severe cases but the relief is only temporary and prolonged use involves risk of undesirable side effects

Perennial allergic rhinitis like hay fever is not dangerous to life but if specific treatment is neglected is often followed by asthma Susceptibility to nasal and sinus infection is also greatly increased

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Asthma

Definition Bronchial asthma is a type of pulmonary incompetency due to constriction of the bronchi and edema of the bronchial mucosa which are caused by the response of an allergically susceptible bronchial tree to specific allergic and/or nonspecific irritative stimuli Typically it occurs in paroxysmal recurrences with intervals of relative comfort but may also assume a mild continuous form with exacerbations or the acute attack may persist for days or weeks as *status asthmaticus*

Etiology Approximately half of the cases of bronchial asthma result from allergy to external antigens most often dusts suspended in the inhaled air but occasionally ingested foods or drugs This type of asthma is usually classed as *extrinsic asthma* The remainder in which no evidence of hypersensitivity to specific allergens is found by skin tests is classed as *intrinsic asthma* Most of the cases in the latter category can be shown to result from infections of the respiratory system

Asthma of the extrinsic type results from the same wheal and erythema type of hypersensitivity as hay fever differing only in the site of the allergic reaction and the two conditions frequently coexist in the same person The reasons for localization of the allergic reaction in the bronchi rather than the nasal mucosa are not established although it has been suggested that inflammation of the bronchial mucosa by intercurrent infections such as acute bronchitis or pertussis or by nonspecific chemical irritants may play a part in some cases

The allergens causing extrinsic asthma are the same as those causing allergic rhinitis By far the most important are inhaled organic dusts such as pollens mold spores animal danders feathers insecticides glue and lint from fabrics Ordinary house dust contains in addition to the substances obviously contributing to its formation other antigens apparently arising from the disintegration of fibers or from contamination with molds and bacteria Although house dust is a complex and variable mixture for most practical purposes an extract of a mixture of dusts from several houses may be used as if it were a single antigen Grain dust flour spices and such vegetable seeds as cottonseed flaxseed and castor bean are important causes in persons exposed as a result of their occupations and occasionally affect those with only casual contact The proportion of cases due to foods is not large but practically any food may occasionally be a cause Among those most active as antigens are eggs fish shellfish nuts spices and chocolate In general the antigens are proteins or similar compounds of somewhat lower molecular weight but certain synthetic drugs such as aspirin may cause severe asthma presumably through acting as haptens

The infections of the respiratory system causing asthma are recurrent or chronic infections of the bronchi often secondary to chronic infections of the paranasal sinuses tonsils or adenoids The sinusitis is usually of the chronic hyperplastic type with purulent secretions only during the more acute phases and is often accompanied by mucous polyps in the nasal cavity or within the sinuses Cultures of the secretions of the respiratory system in such cases usually show a mixed growth with pneumococcus *Streptococcus viridans* and *hemolyticus* *Neisseria catarrhalis* *Klebsiella pneumoniae* and *Hemophilus influenzae* the most common organisms Only occasionally can the etiological importance of a single organism be clearly established

The role of allergy in asthma due to respiratory infection is less obvious than in extrinsic asthma but there is considerable evidence that infective asthma results from

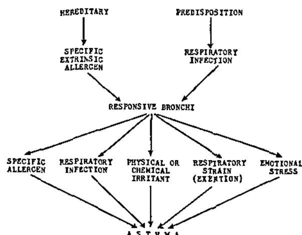


FIG 46

specific hypersensitivity to the bacteria present The asthma may continue severe at times when the infection is in a relatively quiescent chronic stage The symptoms and clinical findings are similar in infective and extrinsic asthma including the abundance of eosinophils in blood and sputum The personal or family history of other diseases due to extrinsic allergy is almost as frequent in infective asthma as in the extrinsic type Skin tests with the available bacterial antigens rarely give immediate urticarial reactions comparable to those produced by pollens and other extrinsic antigens but confirmatory evidence of hypersensitivity is occasionally furnished by the occurrence of an asthmatic attack after the injection of bacterial antigens (usually those derived from cultures of the patient s own secretions) either intracutaneously for skin tests or subcutaneously in attempts at immunization

Although the distinction between extrinsic and infective asthma is useful in the discussion of diagnosis and treatment it is important to remember that many if not most asthmatic patients are affected both by extrinsic allergens and by infective factors Studies of the etiology of a case of asthma should attempt an evaluation of the importance of both extrinsic and infective causes rather than simply classification in one group or the other

Once the asthmatic pattern of reaction has developed through allergy to extrinsic agents or infection paroxysms of asthma may be precipitated by many factors unrelated to the original causes Such secondary factors include emotional stress changes of temperature and humidity irritating fumes or smoke strong odors and physical exertion These factors may be the obvious precipitating causes of individual attacks Their recognition and control play an important part in therapy and in occasional cases in which the underlying allergic or infective basis is obscure or resistant to treatment may constitute the main approach However there is little evidence that true bronchial asthma arises purely from them and when the allergic or infective factors are determined the most satisfactory results usually come from treatment directed at the primary causes In asthma primarily due to extrinsic allergens acute respiratory infections may be a secondary factor precipitating attacks Here also the best results are obtained by treatment directed at the underlying primary cause

Incidence Asthma is a common disease ranking high among the causes of disability in America and Europe Apparently all races are susceptible The incidence in the two sexes is essentially equal and it may occur at any age from early infancy to old age The onset of extrinsic asthma usually occurs in the first four decades of life Infective asthma may begin at any age but more often begins in middle age

Morbid Anatomy The lungs of patients dying during asthmatic attacks are voluminous distended and less elastic than normal The lumina of many of the smaller bronchi are occluded by thick tenacious mucoid secretions The bronchial mucosa and submucosa are thickened Microscopic sections show the alveoli to be distended with thinning and rupture of septums Isolated areas of atelectasis may be present The bronchial epithelium usually shows many goblet cells and the mucous glands in the submucosa are large and active

Pathological Physiology In extrinsic asthma the hypersensitivity is mediated by the skin sensitizing antibody demonstrable in the blood serum by the Prausnitz Kustner reaction and also present in the bronchial tissues and skin Contact of the sensitized mucosa with the antigen which is direct in the case of inhaled allergens and through the blood stream in the case of ingested antigens elicits an antigen antibody reaction in the tissues The exact immunological mechanism of infective asthma has not been established but for the reasons mentioned previously an antigen antibody reaction is believed to be involved

The immunological reaction gives rise to a physiological reaction in the bronchi similar to the nasal reaction in hay fever The lumina of the smaller bronchi are greatly narrowed by swelling of the mucosa and submucosa and by spasm of the bron

chial muscle The narrowed lumina are further obstructed by the secretion of thick tenacious sputum from the bronchial glands

Schild and associates have shown that bronchial muscle excised from the asthmatic patient releases histamine and contracts when exposed to the specific antigen and that this contraction is not inhibited by atropine This suggests that histamine is the chief intermediary between the immunological and physiological reactions although acetylcholine and serotonin may also be involved

In patients subject to asthma attacks similar to those occurring spontaneously may be induced by the administration of either histamine or Mecholyl The same doses of these agents have no effect on normal persons

Although it is apparent that spasm of the bronchial muscle may occur independently of nervous control the reaction in the intact patient is influenced by the autonomic nervous system and by adrenal hormones

Many writers have suggested that reflexes stimulated by irritation of the nasal passages may produce asthma and the influence of psychogenic factors in producing certain attacks in susceptible persons appears to be well established However surgical procedures attempting to prevent asthma by excision of the autonomic nerve fibers supplying the bronchi have not been successful indicating that the nervous factor is rarely predominant It has been suggested that psychogenic factors may produce asthmatic attacks through causing hyperventilation which in itself may precipitate an attack in a susceptible person

The narrowing of the bronchial air passages and further obstruction by mucoid sputum greatly hamper the ventilation of the lungs in both the inspiratory and expiratory phases Increased respiratory effort with utilization of the accessory muscles of respiration tends to increase the efficiency of inspiration more than that of expiration so that the lungs tend to become progressively distended with air as the attack progresses producing an acute emphysema Spirometric tracings made during even mild asthma show a decrease of the vital capacity with the reserve air component greatly decreased or absent after a forced inspiration The maximum breathing capacity is markedly reduced attempts at increased ventilation rapidly increasing the residual air Aeration of the blood is obviously impaired by the ventilatory difficulty and in severe attacks cyanosis may be apparent The heart is relatively little affected except as pre-existing cardiac disease is aggravated by anoxemia

Subsidence of the attack follows widening of the constricted bronchi permitting expectoration of mucous plugs With the obstruction relieved the lungs rapidly return to normal after an acute attack However persistence of even mild asthma over a long period of time may lead to progressive emphysema which is only partially reversible

Symptoms In its most typical form asthma occurs in sporadic paroxysms with respiratory function essentially normal during the intervals Attacks often occur at night but may also follow exposure to a specific allergen unusual exertion a sudden change of temperature a respiratory infection or excitement The onset is marked by a sense of suffocation and pressure in the chest often with a nonproductive cough Respiration is marked by a wheeze which is often audible to the patient and bystanders The respiratory rate is little changed expiration is often prolonged but the respiratory effort is greatly increased The patient sits upright or leans forward to secure maximum use of the accessory muscles of respiration The chest rapidly becomes distended with air and remains in a relatively expanded state at the end of expiration the following inspiratory effort producing little further expansion Termination of the attack is usually marked by cough productive of a considerable quantity of thick stringy mucoid sputum Attacks are often followed by pains in the lower chest apparently resulting from muscle soreness induced by the violent respiratory efforts

Most attacks subside spontaneously in a half hour to several hours In certain cases particularly those in which the asthma follows respiratory infection the acute attack may persist for days or weeks and recur promptly even if temporary relief has been obtained with suitable medications Such persistently severe asthma (status asthmaticus) through fatigue loss of sleep and inadequate nutrition rapidly debilitates the patient

A considerable proportion of patients remain in a chronic state of mild asthma with the symptoms barely noticeable at rest but with dyspnea and wheezing apparent after any exertion a hearty meal laughing singing or emotional excitements Usually these are patients who have had severe acute attacks but occasionally

the onset of the disease is marked by this chronic state with no severe attacks for months or years

Physical signs of asthma are quite characteristic The wheezing may be audible with the unaided ear and is very apparent through the stethoscope with sonorous and sibilant rales heard in all portions of the lung fields usually during both inspiratory and expiratory phases Cyanosis is rarely present in mild cases but may be marked in the more severe attacks The chest shows signs of acute emphysema with a low relatively immobile diaphragm and decreased cardiac dullness

When examined a few hours after cessation of an acute attack the chest may be amazingly normal However in many other cases the persistence of mild chronic *asthma may be manifested by sibilant or* sonorous rales heard chiefly at the lung bases and brought out by cough or forced expiration

Diagnosis The diagnosis of bronchial asthma consists of two steps first the differentiation of asthma from other diseases causing dyspnea and second the determination of the causative agents producing asthma in the particular patient

The differential diagnosis is rarely difficult if the patient is seen during an acute attack The dyspnea the presence of sonorous and sibilant rales throughout the chest the thick tenacious mucoid sputum and the history of periodic attacks are very *characteristic A history of asthma and* other allergic diseases in the family or of previous allergic disease in the patient is valuable contributory evidence

Laboratory examination of the sputum shows distinctive features which are confirmatory evidence The gelatinous globules when smeared on a slide are found to be elongated spiral casts of the smaller bronchi (Curschmann s spirals) Also visible with the microscope are Charcot *Leyden crystals elongated pointed octa*hedral crystals varying in length from 20 to 40 μ Streaks of blood may be visible in the sputum during severe asthma but the occurrence of real hemoptysis is rare and suggests the possibility of some other disease In stained smears eosinophils are seen to comprise a large proportion of the cells When asthma is associated with acute respiratory infection the sputum is intermediate in character between that of simple asthma and the purulent sputum of bronchitis and some of the typical features may be lacking

Examination of the blood usually shows a moderate increase in the proportion of eosinophils ordinarily 5 to 8 per cent but occasionally 30 per cent or higher in severe *infective asthma*

Roentgenograms of the chest show no features characteristic of asthma There may be a moderate increase of the bronchovascular markings and in advanced cases some degree of emphysema is usually apparent They are valuable however to rule out disease of the lung parenchyma cardiac hypertrophy and tumors causing pressure on the trachea or bronchi

The wheezing rales of asthma are usually present throughout the chest during the attack although the sounds may be temporarily suppressed in one area if plugging of a bronchus with mucus has produced atelectasis The persistence of sonor*ous or sibilant rales limited to one portion* of the lungs is suggestive of bronchial obstruction by a tumor foreign body or endobronchial tuberculosis In such cases roentgenograms are of great value but when the differentiation between bronchial asthma and a local obstruction of the air passages is difficult bronchoscopy is indicated

Sonorous and sibilant rales are often heard in patients with acute bronchitis in such cases dyspnea is not a significant symptom and the sputum does not show the characteristic features of asthma Differentiation during the first attack is not always easy and it is important to remem*ber that recurrent attacks* of acute bronchitis with increasingly severe dyspnea often mark the development of true bronchial asthma A sharp distinction between *chronic bronchitis and mild* chronic asthma also is often not possible Many patients with chronic bronchitis show a degree of wheezing dyspnea with typical physical signs of asthma and are benefited by therapy appropriate for asthma such a condition is justifiably described as asthmatic *bronchitis*

Dyspnea due to heart disease only occasionally has the wheezing character of bronchial asthma and sonorous and sibilant rales if present are usually overshadowed by moist or crepitant sounds When severe attacks of cardiac *dyspnea* occur at rest other evidences of heart disease are usually apparent Since both asthma and hypertensive or arteriosclerotic heart disease are common in elderly persons the coexistence of the two conditions is not unusual and the symptoms may be intermingled to a confusing degree

When the diagnosis of bronchial asthma

has been established determination of the etiological factors is essential for rational long term management This requires meticulous inquiry as to the time place and circumstances in which attacks have occurred and the potential allergens to which the patient is exposed Asthma during the spring and summer months suggests pollens or mold spores and a precisely dated season may indicate one particular pollen (See section on Hay Fever for discussion of pollen seasons) Attacks limited to the winter months obviously suggest an infective cause although bedding such as a down quilt used only during the cold weather may be the cause Persistence throughout the year suggests household contacts pets or bedding but may also be due to chronic respiratory infection An observed relationship to certain foods or drugs or to acute respiratory infection is important Certain occupations involve exposure to distinctive antigens the farmer to animal danders feeds and fertilizers the baker to flour and so forth Attacks occurring in certain houses may be due to pets to bedding or upholstered furniture or the molds and fungi they harbor In evaluating the history one should remember that a majority of patients with asthma are affected by more than one factor a large number by both extrinsic and infective factors

The properly taken history usually calls attention to possible antigens but except in cases of pollen asthma only occasionally completely establishes the cause Sensitivity is demonstrated by testing the skin with the possible allergens suggested by the history These skin tests may be carried out by either the scratch or intracutaneous *method as described in the two preceding* sections

In the usual case of asthma intracutaneous tests are made with extracts of pollens animal danders and orris containing 100 protein nitrogen units per ml cottonseed kapok flaxseed and fish glue 10 units and molds house dust feathers silk wool and pyrethrum 1000 units *Foods* are tested in the 1000 unit strength except for egg and mustard 100 units If *the history suggests violent* sensitivity to one or more *antigens* these are tested first in a concentration one tenth as great Not more than six intracutaneous tests are done at one time but if no undue reaction is noted after ten minutes further groups of six may be done to a total of eighteen or twenty four at one sitting Antigens which give doubtful one plus or two plus reactions when tested in dilutions of 10 or 100 units per ml should be retested with successive tenfold increases of concentration until three plus reactions are obtained or until a concentration of 1000 units per ml is reached

If skin tests are properly performed and read the positive reactions indicate sensitization of the skin to the antigens tested The importance of these substances in the actual production of clinical asthma must be judged from correlation of the skin reactions with the history of the case A one plus or two plus reaction which explains the observed time and circumstances of attacks is of value while a strong reaction to a substance with which the patient has little or no contact is of limited significance In general skin reactions to inhaled antigens which come into direct contact with the sensitized mucosa are of greater significance than skin reactions to foods which are greatly altered by cooking digestion and metabolism before reaching the bronchi through the blood stream Positive skin reactions to foods are regarded as suggestive evidence of their etiological importance in asthma and the final evaluation is by clinical judgment based either on the past history or the observed results of eliminating the foods from the diet Not only may foods giving positive skin reactions prove innocuous when eaten but occasionally foods showing negative skin reactions cause asthmatic attacks usually delayed several hours after ingestion and presumably due to the production by digestion of an antigen not present in the original material This situation while rare obviously calls for careful observation rather than acceptance of skin tests as the *final criterion*

Evaluation of infective factors in the causation of asthma is not always easy Attention may be directed to this possibility by the absence of skin reactions to all probable extrinsic allergens but in many cases both extrinsic allergens and infection are important As previously noted the onset of asthma after the age of 40 years is statistically suggestive of infective asthma at any age the coexistence of chronic sinusitis particularly of the hyperplastic type or of nasal polyps indicates a potential infective factor Skin tests with bacterial antigens have not proved a reliable criterion except in those cases in which an exacerbation of constitutional symptoms is inadvertently produced In patients requiring hospitalization the persistence of asthma after three or four days

in an environment which eliminates inso far as possible contact with inhalant allergens usually indicates the presence of endogenous usually infective factors

As previously mentioned asthmatic patients are often made worse by nonspecific secondary factors such as changes of temperature and humidity irritating fumes and odors acute infections exertion excitement and emotional stress These conditions rather than changes in exposure to antigens may be the actual precipitating causes of individual attacks Their importance which can be judged only by careful inquiry into the circumstances of occurrence of exacerbations must be evaluated if treatment is to be successful However obvious as their relationship may be *they should be recognized as secondary influences and not confused with the fundamental allergic or infective causes of the asthmatic state*

Prognosis Asthma is a chronic disease with a marked tendency to periodic recurrence over a period of many years unless the causative factors are recognized and satisfactorily handled Present methods of treatment do not afford the prospect of actual cure Approximately 25 to 30 per cent of the cases beginning in early childhood undergo spontaneous recovery during adolescence but since an essentially equal number become worse during the same period withholding treatment in hope that the condition will be outgrown is not justified During adult life the tendency to spontaneous recovery is much less marked and there is a greater probability of the attacks becoming progressively more frequent and prolonged with the remission less complete and with nonspecific factors playing an increasing part in the causation With repeated attacks over a period of years asthma originating as a strictly seasonal reaction to a specific pollen may be prolonged progressively beyond the pollen season and gradually enter into a chronic state lasting throughout much of the year *Infective asthma in elderly patients is particularly apt to become chronic* Persistent asthma from any cause is apt to produce pulmonary emphysema and permanent ventilatory disability

The danger to life in the average attack is slight although death occasionally occurs in acute attacks caused by allergy to rapidly absorbed drugs such as aspirin or in attacks resulting from injection of an overdose of antigen in testing or treatment However in severe status asthmaticus with persistent cyanosis failing to respond to corticotropin or cortisone the mortality is considerable Some deaths are attributable to depression of respiration and cough by injudicious use of sedatives but many are entirely uninfluenced by attempts at therapy

Treatment Therapy of asthma comprises three types of efforts (1) symptomatic relief of the attack (2) control of specific causative factors (3) general care of the patient

Symptomatic Relief During the acute attack relief may usually be attained with epinephrine 1 1000 injected subcutaneously or intramuscularly Since patients vary both in tolerance and response best results are obtained with 0 3 to 0 5 ml (0 1 to 0 2 ml for infants or small children) *repeated if necessary every five or ten minutes for two or three doses* This treatment will terminate mild attacks but in more persistent cases may be required every two or three hours Frequent repetition may be avoided by the use of a slowly absorbed form of epinephrine such as epinephrine in oil 1 500 1 ml intramuscularly every six to twelve hours For the ambulatory treatment of patients with frequent mild attacks *inhalation of an aerosol* of epinephrine 1 100 or isopropylarterenol (Isuprel) 1 200 from a suitable nebulizer is a convenient measure often producing prompt relief Also effective in mild attacks and having the advantage of oral administration is ephedrine 25 mg every four hours if necessary The stimulating effects of ephedrine may be minimized by combination with a mild sedative such as phenobarbital 15 mg *All drugs of the epinephrine group should be used cautiously in patients with coexisting hypertension heart disease or hyperthyroidism*

In acute attacks not relieved by epinephrine aminophylline 0 25 to 0 5 gm injected slowly intravenously is often effective and may be repeated after two to three hours if necessary A slower but more prolonged effect may be obtained by *administering aminophylline* 0 5 gm (0 25 for children) by rectum every eight to twelve hours if needed either as a suppository or dissolved in 20 to 30 ml of water Oral use of aminophylline in asthma is limited by the tendency of adequate doses to produce nausea However a combination of aminophylline 120 mg ephedrine 25 mg and phenobarbital 15 mg every four hours if necessary is useful for mild attacks

Sedatives are useful adjuncts in the relief of severe asthma but the danger of

depressing respiratory function precludes their employment as the principal therapy Demerol is preferable to morphine and may be used in doses of 50 mg repeated once after four hours if necessary The barbiturates and tranquilizers in moderate doses are valuable If strong sedation is needed ether 60 ml in 120 ml of oil by rectum is relatively safe Codeine 15 mg or elixir of terpin hydrate with codeine 5 ml every four hours may be used to control excessive cough

In persistent asthma expectorants are often valuable to facilitate discharge of tenacious mucoid sputum The most effective is potassium iodide 0 6 gm three times a day after meals Ammonium chloride in the same doses may be tried by patients who do not tolerate iodide

In severe asthma which is not readily controlled by medications oxygen administered by tent nasal catheter or mask is a useful supportive measure Positive pressure is of value only in the inspiratory phase the ordinary masks applying pressure during the expiratory phase are not helpful

If acute asthma persists for several days or fails to respond to the medications previously mentioned the use of corticotropin cortisone or prednisone is of value for temporary relief In the most severe cases corticotropin 15 to 20 units is given in an intravenous drip of 1 liter of 5 per cent glucose solution over a period of eight hours repeated daily if necessary In less urgent situations corticotropin 40 units in gelatin is injected intramuscularly daily or cortisone 50 mg or prednisone or prednisolone 10 mg given by mouth every six hours As soon as relief is obtained the dose is reduced by 25 to 50 per cent and then rapidly tapered off over a period of four to five days These drugs must be used with caution in patients with heart disease diabetes peptic ulcer or mental disease and are generally contraindicated in patients with pulmonary tuberculosis or pregnancy Careful observation for evidence of fluid retention is essential particularly if cortisone or corticotropin is continued for more than a week Salt intake should be restricted and potassium chloride given in 1 0 gm doses three to five times daily

In severe chronic asthma which cannot be controlled by other symptomatic or specific treatment the use of small maintenance doses of prednisone or prenisolone over a prolonged period may be considered if the disability caused by the asthma outweighs the potential risks of a prolonged hyperadrenal state After the symptoms have been controlled by the usual doses of prednisone or prednisolone the dose is reduced to the minimum which will maintain a satisfactory degree of relief usually not exceeding 5 mg every eight to twelve hours Patients receiving such treatment should be kept under close supervision and intercurrent infections treated promptly

Numerous other measures are of some value in various phases of asthma In persistent severe asthma with retention of thick sputum bronchoscopic aspiration is sometimes effective Fever therapy usually produced with intravenous typhoid vaccine has been used in status asthmaticus but is rarely as effective as cortisone or corticotropin For the relief of mild attacks inhalation of the fumes of burning stramonium leaves is reasonably effective The antihistamine drugs are also mildly efficacious but offer no advantage over ephedrine and aminophylline

Specific Treatment Satisfactory handling of asthma over the long term requires the control of the causative factors Asthma due to extrinsic antigens is best treated by the avoidance of contact with the antigen when possible Elimination of household pets feather pillows and so forth generally produces more satisfactory relief than any attempt at immunization In the case of occupational allergens such as flour in baker s asthma a trial of injection treatment may be warranted but usually a change of occupation eventually proves necessary Avoidance of windborne pollen is possible as a temporary measure either by a trip to a location free of the offending plant or by air filtration but continuation of the patient s usual residence and activities requires injection treatment Contact with house dust may be minimized by stripping the bedroom of carpeting drapes and heavy furniture and by careful cleaning but coincident injection treatment is usually needed

Treatment by injections of antigen variously described as immunization desensitization or hyposensitization is generally indicated in asthma due to house dust mold spores or pollens and may be advisable in the cases due to other protein antigens with which the patient cannot completely avoid contact The general principle is to begin treatment with an injection of no more than twice the actual amount of antigen injected in the intracutaneous test giving a moderate (two plus) or marked (three plus) skin reaction and to proceed with injections once or twice a

week gradually increasing the dose aim ing to reach a dose approximately 500 times the initial one after about sixteen injections The schedules included in the section on Hay Fever are generally ap plicable to the treatment of asthma but in patients highly sensitive to nonseasonal allergens it may be necessary to proceed somewhat more slowly if the patient is constantly exposed to the antigen while treatment is progressing In the case of house dust allergen the strengths of avail able solutions may not permit as great a range of dosage as with pollens Usually a top dose of 0 5 to 0 8 ml of the strongest available dust extract is adequate

The injections are given subcutaneously on the lateral aspect of the upper arm or thigh with a rubber tourniquet and epi nephrine hydrochloride 1 1000 solution at hand in case of an excessive reaction After the injection the patient should be kept under observation for twenty minutes to observe the local reaction and to treat any constitutional symptoms that may de velop (See section on Hay Fever)

While the antigen dosage schedules serve as a guide they must be modified in ac cordance with the individual patient s reac tion As the dosage progresses a local reaction manifested by redness and swell ing 2 to 4 cm in diameter usually occurs at the site of injection and need not cause a change in the program of doses If the local reaction is uncomfortably large or persists for more than thirty six hours the same dose should be repeated at the next injection rather than progressing accord ing to the schedule When this dose no longer produces an excessive reaction one may increase as indicated in the schedule or somewhat more cautiously If an injec tion produces a constitutional reaction the following dose should not exceed one half the dose producing the reaction and should not be given sooner than one week later Subsequent increases should be about one half as large as those listed in the sched ules with careful observation of the local reaction each time If it becomes apparent that the patient cannot tolerate a larger dose the schedule is abandoned and treat ment continued with a dose one quarter to one third less than that which produces an excessive reaction

The maintenance dose either the top dose indicated in the schedule or that comfortably tolerated by the patient is re peated every two weeks If the symptoms are completely controlled the interval be tween injections may be increased to three or four weeks the individual doses remain ing the same Treatment may be expected to be necessary for several years or indefi nitely Once a year the skin tests with anti gens used in treatment are repeated and if some have become essentially negative those antigens may be discontinued while carefully observing the patient for recur rence of symptoms

Treatment of Infective Asthma Infec tions of the respiratory system believed to be causative factors in asthma should be treated vigorously with available medical and surgical measures During the more acute stages the antibiotics penicillin tetracycline and streptomycin are often effective It should be noted that asthmatic patients are particularly susceptible to severe penicillin reactions Adequate drain age of infected paranasal sinuses should be maintained by local treatment with excision of nasal polyps if necessary If recurrences of infection are very frequent prophylactic doses of benzathine penicillin 600 000 units every two weeks or of a sulfonamide such as sulfisoxazole (Gantri sin) 0 5 to 1 0 gm twice a day may be given during the fall and winter months

Injections of bacterial vaccines or fil trates are often of value in recurrent infec tive asthma but must be given cautiously in patients highly allergic to bacterial products General reactions with exacerba tions of asthma often delayed one or two days after the injection and lasting several days are easily provoked by excessive doses If the concentrated vaccine is 1 per cent by volume or approximately 5 billion organisms per cubic centimeter the first dose should not exceed 0 1 ml of a 1 1000 dilution and subsequent doses at weekly intervals may be gradually increased up to 0 1 to 0 2 ml of the concentrated material in a manner similar to that employed for pollen antigens

If the sinuses show evidence of chronic disease and conservative measures are not effective consideration may be given to surgical measures Since the thickened membrane of the sinuses is the site of in fection satisfactory surgical treatment re quires widely opening all the sinuses shown by roentgenograms to be involved and com plete removal of the hyperplastic or poly poid membrane When such operations are thoroughly performed the results are favor able in a sufficient proportion of cases to warrant their employment in cases not otherwise relieved

General Measures The general care of the asthmatic patient involves chiefly the

avoidance of those secondary factors which are apt to aggravate asthma regardless of the primary cause Extremes of cold and humidity should be avoided particularly outdoor exertion in cold damp weather Exposure to respiratory infections should be avoided as far as reasonably possible For these purposes spending the winter in a warm dry climate may be helpful Smoking should be avoided or restricted to a minimum Physical exercise should be limited to the tolerance of the patient and the more violent forms of exertion should be avoided Causes of emotional stress should be eliminated when possible psychotherapy is only occasionally needed

In patients with chronic asthma who are developing emphysema breathing exercises which stress complete expiration rather than deep inspiration are helpful both to increase ventilatory efficiency and to lessen the development of chest deformity Manual pressure on the lower ribs and diaphragm during expiration is helpful in emptying the chest

Maintenance of an optimistic mental state is important Needless to say few things will contribute more to this attitude than the combination of effective and readily available symptomatic relief with a logical plan for determining and coping with the causative factors

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Drug Allergy

Definition Drug allergy is a general often loosely used term for a multiplicity of sensitivity reactions including skin eruptions edema arthritis lymphadenopathy hematological abnormalities fever and periarteritis which occur during or following the administration of a variety of therapeutic agents The symptoms bear no relation to the primary pharmacological properties of the drug concerned and resemble in important respects the manifestations of serum sickness It is generally assumed that the reactions are due to the presence of antibody against the drug itself or against an antigenic conjugate between the drug and a protein in the blood or tissues This assumption is based in part on experimental studies by Landsteiner and his associates of the antigenicity of simple chemicals and there is some evidence to support it in several types of reaction in human beings However in actual practice the majority of reactions cannot be proved to involve an antigen antibody mechanism Some of the manifestations attributed to allergy such as agranulocytosis hemolytic anemia and hepatitis cannot be reproduced in experimental animals nor can the presence of antibody be demonstrated in patients The designation of such reactions as drug allergy should therefore be regarded as tentative

Incidence Although allergic reactions have been reported to occur with almost every medication in common use there are large differences in the capacity of different drugs to produce reactions Important differences also exist in the susceptibility of different persons patients with a history of other allergic diseases are more apt to develop drug reactions As an example aspirin rarely causes sensitization in normal persons but patients with bronchial asthma are remarkably prone to exhibit asthma or urticaria after taking the drug The incidence of penicillin reactions has been stated to be as high as 10 or 15 per cent but there is a great variation in different reports depending on the degree of purity of the penicillin the presence of other substances in the vehicle employed the route of injection the duration of treatment and the amount administered At the University of Minnesota Hospitals 2 5 per cent of a recent series of 562 patients developed reactions to penicillin consisting of skin eruptions and mild fever no severe reactions occurred

Certain drugs such as phenylethylhydantoin (Nirvanol) arsphenamine and thiouracil are known to produce sensitivity reactions in a high proportion of patients "Nirvanol sickness a syndrome closely resembling serum sickness has been reported to occur in all patients given large doses of the drug

The incidence of drug allergy depends to some extent on prior exposure to the drug although this seems to be much less im

portant than in serum sickness Reactions to the sulfonamides and penicillin are more likely to occur in previously treated patients but many occur at the first contact with the agents

Pathogenesis Landsteiner and his associates made a series of important experimental observations which have led to an interesting concept of the mechanism of drug allergy It was shown that animals could be specifically sensitized to simple chemical compounds such as picric acid or dinitrochlorobenzene by repeated exposure to the substances or by the injection of conjugates of the chemicals with protein Sensitization with chemical alone was found to involve a union *in vivo* with body protein yielding antigenic complexes whose immunological specificity was determined by the chemical haptene Antibody formed against such complexes was capable of reacting either with the chemical alone or with the chemical protein conjugate but not with the protein

It has been postulated that a similar mechanism may account for drug allergy in man The administration of a drug would under this theory be followed by the formation of a union between tissue or blood proteins and the drug or a breakdown product of the drug Antibody produced against the conjugate would subsequently react with the drug itself (or with the breakdown product) and also with protein drug conjugate formed after readministration of the drug Moreover since specificity of the antibody is determined by the structure of the chemical haptene it is possible that sensitization would also occur to closely related substances

If this concept is correct the mechanism of drug allergy would involve several variable factors which might affect the incidence of reactions and also the tissue sites involved The capacity of a drug to unite with body protein and differences in the degree of union in different individuals would be of much importance If the complex of drug and body protein were soluble and rapidly absorbed the sensitivity would probably be of the immediate anaphylactic type If the protein constituent of the complex were confined to a particular tissue or cell and not removed or absorbed reactions of the local delayed type would occur Furthermore if the haptene were not the drug itself but a metabolic breakdown product individual variations in the metabolism of the substance would play a role in the incidence of drug allergy

Further investigation of the problem in man has been delayed because of the absence of satisfactory methods for detecting the presence of antibody in almost all types of drug allergy Ackroyd has described a complement fixation reaction with the serum of patients with thrombocytopenia due to Sedormid sensitivity in which the antigen consists of a mixture of Sedormid and platelets no fixation of complement occurred with Sedormid alone or with platelets alone Leftwich reported that sulfonamide sensitivity could be detected by an intradermal injection of serum containing the sulfonamide but not with solutions of sulfonamide alone implying that a protein sulfonamide complex was necessary for the production of a skin reaction However a large number of investigators have been unable to demonstrate antibody in various types of drug allergy by any of the available methods

Pathology Death is a rare event in drug allergy and there is little information concerning the pathology of the disease Rich and his associates found typical vascular lesions of periarteritis nodosa similar to the changes in experimental serum sickness in several patients with severe reactions to sulfonamides Similar lesions have been described in patients dying with hypersensitivity reactions to penicillin iodine thiourea and Dilantin

Symptoms The most common type of drug reaction is a mild systemic illness with the clinical features of typical serum sickness including erythematous and urticarial *skin eruptions arthralgia* or *arthritis lymphadenopathy* and *fever* Such reactions may occur during treatment with penicillin the sulfonamides chlortetracycline streptomycin aspirin barbiturates Dilantin thiouracil iodides and many other drugs The disease usually begins between six and twelve days after the start of medication and lasts two or three days More prolonged reactions may occur if the drug is not withdrawn promptly

Immediate anaphylactic type reactions to drugs are uncommon but occasionally occur in patients with extreme degrees of sensitization persons with other allergic diseases are more susceptible to such reactions The symptoms which are similar to those of an acute serum accident may appear within a few minutes after injection *of certain drugs Some of the acute fatal* reactions to penicillin are of this type Procaine produces a similar reaction in susceptible individuals it is not known whether this is based on allergy or a pharmacological idiosyncracy

Isolated symptoms are common in drug allergy Patients may develop only fever without other allergic manifestations usually during the second week of treatment with penicillin sulfonamides arsphenamine iodides and barbiturates The fever continues until the drug is discontinued and will usually reappear with a second administration Other isolated signs of drug allergy may be skin eruption conjunctivitis lymphadenopathy abdominal pain and vomiting and pharyngitis Proctitis and diarrhea are frequent complications of treatment with chlortetracycline oxytetracycline and chloramphenicol but there is no evidence that this represents an allergic reaction

Other forms of skin eruption differing from the erythema and urticaria of serum sickness occur as reactions to certain drugs *Exfoliative dermatitis* is a complication of treatment with gold arsphenamine penicillin iodide quinine Dilantin and the sulfonamides *Fixed eruptions* which recur in the same skin area on readministration of the drug are caused by numerous drugs including barbiturates phenolphthalein bromide iodide sulfonamides and Bromsulfalein *Erythema nodosum photosensitization* and *contact dermatitis* have occurred as reactions to various drugs

The hematological reactions to drugs are of major importance The most frequent and serious of these is *agranulocytosis* which may occur during treatment with the sulfonamides thiouracil aminopyrine arsphenamine Butazolidin and gold Agranulocytosis usually appears during or after the fourth week of continuous treatment the onset may be earlier in previously sensitized patients *Thrombocytopenic purpura* has been associated with Sedormid quinine quinidine thiouracil Mesantoin and the sulfonamides *Hemolytic anemia* was a frequent complication of treatment with the older sulfonamide preparations particularly sulfapyridine and sulfanilamide hemolysis usually occurred within the first five days of treatment and was not proved to be due to allergy *Aplastic anemia* is an infrequent event during therapy with chloramphenicol gold trimethadione and the sulfonamides the allergic basis for this complication is also open to question

Periarteritis nodosa has occurred during treatment with the sulfonamides penicillin iodine thiourea and Dilantin The studies of Rich and his associates indicate that this disease may represent a basic type of hypersensitivity reaction to many antigenic substances

Severe *liver damage* is sometimes produced by arsphenamine cinchophen and the sulfonamides There is no direct evidence to indicate an allergic basis for such reactions The same is true for *peripheral neuritis* and *hemorrhagic encephalitis* which are rare complications of drug therapy It is possible that the latter diseases may occur as manifestations of periarteritis nodosa

Longcope has emphasized the importance of renal involvement in drug allergy Acute *hemorrhagic nephritis* has appeared during reactions to Nirvanol arsphenamine and the sulfonamides

A syndrome resembling *lupus erythematosus* with arthritis fever polyserositis and hyperglobulinemia has been described in patients receiving prolonged therapy with hydralazine (Apresoline) for hypertension The plasma of these patients produced the characteristic alteration of leukocytes which occurs in lupus (the L E phenomenon) which has also been observed in allergic reactions to penicillin

Diagnosis Discontinuation of the drug in question is the safest and most reliable diagnostic measure and the prompt disappearance of symptoms permits a presumptive diagnosis of drug allergy There are no specific diagnostic tests of proved value If symptoms recur when the drug is administered a second time the diagnosis becomes more certain but this procedure is rarely justified Skin tests and attempts to demonstrate antibody by test tube or passive transfer are negative in most instances Eosinophilia may occur in patients with skin eruptions and the L E phenomenon may be present in severe systemic drug reactions

Treatment In most cases the symptoms are completely relieved when the medication is stopped and no other treatment is required In mild reactions and when the therapeutic agent is of vital importance the medication may be continued under close observation but if another drug can be substituted this should always be done Agranulocytosis should be treated with appropriate antibiotic therapy to control infection Benadryl or Pyribenzamine in a dose of 50 mg every four hours may relieve the itching and discomfort of skin eruptions Epinephrine should be given for immediate anaphylactic reactions in a dose of 0 5 to 1 0 ml of the 1 1000 dilution by subcutaneous injection it is also useful for temporary relief of urticaria

Corticotropin and cortisone may be of great value in the treatment of severe reactions Either of these hormones in a dose of approximately 100 mg daily should be used in cases of exfoliative dermatitis prostrating or extremely painful systemic reactions and inflammatory reactions involving the eye Considerably larger doses of cortisone or hydrocortisone may be required for a short period of time in severe cases

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Serum Sickness

Definition Serum sickness is the systemic reaction which follows an injection of foreign serum and is the result of interaction between specific antibody and an antigenic protein or proteins contained in the injected serum In its fully developed form the illness is characterized by skin eruptions fever lymphadenopathy arthralgia abdominal pain nausea and vomiting It may occur at any time within two weeks after the injection of serum In persons previously sensitized to the foreign protein the antibody response is accelerated and the incubation period is several days shorter than in normal persons With sufficiently high degrees of preexisting sensitization an extremely severe and sometimes fatal reaction may occur immediately after injection such reactions are commonly referred to as *serum accidents*

Incidence The introduction of prophylactic toxoids and specific antibacterial therapeutic agents has greatly reduced the use of serum therapy and therefore the incidence of serum sickness The disease now occurs as an occasional complication of the management of diphtheria tetanus clostridial infections botulism and snake venom poisoning The incidence of reactions is greater after injections of whole horse serum than when highly purified antiserums are employed presumably because of the reduced number of different antigens in the latter preparations

Neither age sex state of health nor route of injection appears to influence the incidence of serum sickness There is some evidence that Negroes and American Indians are less susceptible than white persons The major factors which determine the incidence as well as the severity of the disease are (1) the amount of serum injected and (2) the previous immunological status of the patient

When the amount of serum is 10 ml or less serum sickness occurs in approximately 10 per cent of patients The incidence rises to 90 per cent when 100 ml or more are injected Patients with a history of previous injections of the same foreign serum may be expected to develop serum sickness more frequently and in greater severity than normal persons

Instances of serum sickness have occurred following transfusion with human whole blood Some of these are due to passive transfer of antibody against antigens to which the recipient of the transfusion is exposed others have been shown to be caused by the presence of antigens in the transfused blood to which the recipient is hypersensitive

A syndrome which is indistinguishable from serum sickness is known to occur during the course of treatment with certain drugs and it is possible that a similar immunological disturbance is involved This type of reaction is discussed in the section on Drug Allergy

Pathogenesis The basic mechanisms which are responsible for serum sickness have received much investigation in man and in experimental animals It is known that within six to twelve days after an injection of foreign protein in the rabbit precipitating antibody appears in the blood In subjects previously exposed to the same antigen antibody may appear within the first two or three days Simultaneously with the appearance of antibody the foreign protein which has been detectable in the blood until this time disappears completely It has been suggested that a precipitation reaction between antigen and antibody followed by clearance of the conjugate from the blood may be occurring during this period The mechanism of removal and

destruction of the antigen is not understood The level of serum complement undergoes a sharp reduction during the time of appearance of antibody and disappearance of antigen from the blood perhaps this is a manifestation of fixation of complement *in vivo*

Comparable events have been observed in human serum sickness and it is generally accepted that a causal relationship exists between the antigen antibody interaction and the symptoms of the disease A correlation has been shown to exist between the occurrence of serum sickness and the degree of antibody formation although the antibody is usually not demonstrable until late in the course of the illness Patients who do not develop serum sickness have little or no demonstrable antibody and the antigen is demonstrable in the circulating blood for much longer periods of time As to the actual events which lead to tissue damage in serum sickness there is very little information It has been suggested that injury to endothelial and smooth muscle cells may be caused by the local release of histamine acetylcholine or proteolytic enzymes direct proof for these hypotheses is lacking

Recurrences of symptoms sometimes occur after apparent recovery from serum sickness These relapses which are usually seen in patients given whole horse serum probably represent successive independent episodes of antigen antibody interaction involving different antigenic proteins in the serum

Pathology Serum sickness is almost always a relatively benign brief illness and very few deaths resulting from the disease itself have been recorded The most important information concerning the pathological alterations in tissues has been contributed by Rich and his associates who described vascular lesions indistinguishable from those of periarteritis nodosa in patients with serum sickness Similar arterial lesions have been shown to occur frequently in experimental animals following the intravenous injection of large amounts of foreign protein On the basis of these observations it has been suggested that periarteritis nodosa and related "collagen" diseases such as rheumatic fever and disseminated lupus erythematosus may be based on an immunological disturbance analogous to serum sickness

Symptoms The incubation period is usually between six and twelve days after the injection of serum but may be much shorter in previously sensitized persons The illness begins with a *skin eruption*, which may take the form of urticaria patches of erythema or a diffuse morbilliform rash or combinations of these Such skin manifestations are the most conspicuous and constant feature of the disease and occur in over 90 per cent of patients Occasionally petechiae or purpuric skin lesions are encountered *Itching* occurs shortly before the skin eruption is obvious and usually persists throughout the illness it is most bothersome in patients with extensive urticarial lesions A generalized *lymphadenopathy* is present in most patients at the time of or just prior to the appearance of the skin eruption *Edema* of the face eyelids hands and feet occurs in approximately 30 per cent of cases It is more frequent and severe in children than in adults Edema of the glottis is in rare instances sufficiently intense to require tracheotomy Some patients without obvious edema undergo a rapid *gain in weight* during the period of the disease owing to retention of water The renal excretion of sodium chloride and water is markedly reduced at this time

In many patients the disease is limited to the above mentioned manifestations and these disappear within two to three days In more severely ill patients the skin eruption lasts for a week or longer and on the third or fourth day after onset *fever* appears with daily elevations of temperature to 101° or 102° F During the febrile period constitutional symptoms such as *malaise headache abdominal pain nausea* and *vomiting* are often present

Involvement of the joints occurs in approximately 50 per cent of patients with serum sickness usually beginning two to three days after the appearance of skin eruption There may be mild *arthralgia* and some stiffness on movement or less commonly there may be outright *polyarthritis* resembling the joint symptoms of acute rheumatic fever Swift and Boots found the joint fluid to be an inflammatory exudate containing numerous polymorphonuclear leukocytes The earliest joint to be involved is usually the temporomandibular pain and limitation of motion in this joint may be misinterpreted as early tetanus in patients treated with antitetanus serum

Neurological manifestations sometimes occur in severe serum sickness *Stupor coma* and transient *hemiplegia* associated with an increase in cerebrospinal fluid pressure have been observed *Optic neuritis* may occur as a complication of serum sickness *Peripheral neuritis* usually in

volving the cervicobrachial plexus may cause severe root pains in the shoulder girdle and upper extremities with temporary weakness or paralysis of arm muscles

Diagnosis Laboratory studies provide little if any assistance Patients with serum sickness following injections of horse serum may exhibit elevated titers of heterophile antibody for sheep erythrocytes Leukocytosis and eosinophilia are uncommon but may occur late in the course of illness The urine may show slight albuminuria and a few casts but there are no significant evidences of renal impairment The erythrocyte sedimentation rate is usually normal

The disease *may be mistaken for rheumatic* fever if a history of serum administration is unobtainable In cases of inconspicuous or absent skin eruptions the symptoms may resemble those of complications of the disease for which serum was administered for example tetanus In general however the typical syndrome of serum sickness is unmistakably recognizable

Serum Accidents *The acute immediate* shock like reactions which follow an injection of foreign serum in previously sensitized individuals are in all probability based on the same immunological disturbance as that involved in serum sickness The early onset and severity of symptoms are due to the existence of antibody at the time of injection of antigen and the situation is *quite similar to anaphylactic shock in animals* Within a few seconds after injection the patient may exhibit extreme apprehension violent itching sneezing and coughing and asthmatic breathing Generalized urticaria may appear within minutes The blood pressure falls and the pulse becomes weak or imperceptible There may be sudden loss of consciousness accompanied by generalized convulsive seizures The temperature is usually elevated shortly after the beginning of symptoms Death can occur within less than ten minutes or after several hours Patients who survive such episodes usually *exhibit other evidences* of typical serum sickness during the next few days

The pathological findings in fatal serum accidents include extensive acute emphysema of the lungs dilatation of the right ventricle and multiple small hemorrhages in the heart lungs kidneys and adrenal glands

Treatment Recognition of hypersensitivity in patients prior to the administration of foreign serum is of the first importance in avoiding serum reactions All patients should be carefully questioned concerning previous injections of serum A history of asthma hay fever or other allergic reactions is an indication for special caution in the administration of serum *All* patients regardless of history should be tested for cutaneous and conjunctival *sensitivity before undertaking serum treat*ment The intracutaneous test may be performed with 0 02 ml of a 1 10 dilution of the serum to be used for the conjunctival test a drop of 1 100 dilution is employed If either test is positive the use of serum treatment should be reconsidered in the light of the potential danger involved If it is imperative that serum be administered *an attempt should be made to desen*sitize the patient This may be done by giving repeated injections of small amounts every fifteen minutes starting with 0 1 ml of a 1 100 dilution subcutaneously and doubling the amount with each dose until 1 ml has been given by this route Intravenous injections are then begun in the same fashion beginning with 0 1 ml and *doubling the dose every fifteen minutes* until the required amount has been administered

Serum reactions of the immediate anaphylactic variety are treated with epinephrine which should be available in a syringe whenever serum is injected A dose of 0 5 to 1 0 ml of a 1 1000 dilution should be given subcutaneously at the first sign of an *acute serum reaction* and repeated after a few minutes if indicated

The usual case of serum sickness is a mild self limited disease presenting few problems of therapy The itching discomfort associated with urticaria may *be tem*porarily relieved by subcutaneous injections of epinephrine or by the oral administration of Pyribenzamine in a dosage of 50 mg every four hours Cortisone and prednisone have been used with success in the treatment of allergic reactions to drugs and may be useful in controlling the discomfort in severe or prolonged attacks of *serum sickness most cases* however are so mild that such treatment is unnecessary

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Contact Dermatitis

Definition Contact dermatitis is an eczematous inflammation of the skin resulting from exposure of its unbroken surface to foreign material It may result either from the primary irritant effect of the causative agent or from a specific acquired allergic sensitization to an agent which is not irritating on first contact Although these two types of reaction produce similar pathological changes in the skin the former represents a response of essentially all persons to an obviously toxic agent and the latter is a specific response of a sensitized individual to a substance which does not cause irritation on the first exposure and even after repeated exposure affects only certain persons It should be noted that many industrial chemicals which in high concentrations act as primary irritants are also active sensitizers in dilutions which are not toxic Since the primary irritants encountered in the home—lye solvents strong acids and tincture of iodine—are well known and those used in industry are familiar to workers handling them it is the allergic type of contact dermatitis which will be discussed here

Etiology The agents producing allergic contact dermatitis must be capable of penetrating the unbroken surface of the skin and eliciting a specific allergic response Most of the typical antigens which produce other types of allergic reactions are large molecules proteins or complex carbohydrates Since these compounds do not readily penetrate the epidermis they rarely act as causative agents of contact dermatitis The principal etiological agents are of relatively small molecular size but act as haptens combining with the proteins of the skin and producing conjugates of sufficiently altered immunological specificity to be antigenic to the individual in which they are formed

The actual causative agents are innumerable and of varied chemical nature Important examples which may be encountered at home are (1) metals particularly nickel chromium and mercury (2) salts of these and other metals (3) topical medications particularly sulfonamides local anesthetics and antihistamines (4) cosmetics nail polish and hair dyes (5) soaps and detergents (6) dyes and finishes applied to fabrics furs or leather (7) plastics (8) rubber and (9) oleo resins of plants particularly those of the genus Rhus (poison ivy and poison sumac) Chemical workers photographers metal workers beauticians tanners nurses and others encounter other agents peculiar to their occupations

The susceptibility of different persons to sensitization varies either because of differences in the permeability of the skin or for immunological reasons In experimental animals Chase has shown that heredity is an important factor in susceptibility No such hereditary influence is apparent in clinical practice and contact dermatitis is not related to the familial predisposition to allergies of the asthma and hay fever group Skin which is already inflamed by burns or pre-existing eczema is more susceptible to sensitization than normal skin

Pathogenesis and Morbid Anatomy Allergic contact dermatitis is an example of the delayed type of allergic reactions As in other allergies of this group no antibody is demonstrable in the serum or plasma of the sensitized person In contact dermatitis of guinea pigs sensitization is readily transferred to normal animals by injection of lymphoid cells This phenomenon is believed to reflect the presence of a type of antibody fixed in the cells but is not readily demonstrated in man

With active sensitizing agents allergy may be produced in a majority of persons by a single application to the skin There is no visible reaction to this contact After an incubation period of ten to twenty days the entire surface of the skin is sensitized and responds to a second application with dermatitis developing in twenty four to forty-eight hours Experimental studies indicate that the causative agent combines with protein of the skin to form a conjugated antigen which passes through the lymph to lymph nodes and other organs of antibody formation Antibodies which are formed become fixed in the skin and these give rise to the specific reaction on subsequent contact with the hapten protein conjugate

The reaction is first manifested by erythema and swelling of the skin due to intercellular and intracellular edema This progresses to the formation of vesicles and blebs which are easily ruptured by scratching to produce a raw oozing surface In this stage secondary infection particularly by staphylococci is common In chronic cases the skin may become thickened (lichenified) by scratching The lesions do not resemble the wheals produced by histamine and their development is not inhibited by antihistaminic drugs The lesions

contain histamine in far greater concentrations than normal skin but the role of histamine in pathogenesis is not clear

Symptoms The lesions usually become apparent within twenty four hours after exposure as redness and edema of the skin progressing to vesicles varying from pin point size to blebs several centimeters in diameter They are at first limited to the area of contact but in cases of severe sensitivity may be spread to new areas by scratching The site of the dermatitis depends upon the causative agent and type of contact but the palms soles and scalp are rarely affected The inflammation of the skin may be accompanied by subcutaneous edema particularly when the face or genitalia are affected The chief subjective symptom is itching or burning of the involved skin The general health is rarely affected

Differential Diagnosis Other common eczematous lesions to be differentiated from contact dermatitis are

1 *Atopic dermatitis* the chronic recurrent eczema often beginning in infancy and usually associated with a personal or family history of hay fever or asthma This characteristically involves the antecubital and popliteal fossae neck and wrists Vesiculation is rare and lichenification usually marked

2 *Seborrheic dermatitis* typically involving the scalp postauricular and nasal folds associated with an oily skin and manifested by greasy scales with only mild erythema

3 *Fungus infections* of the skin particularly involving the skin folds between the toes in the groin and beneath the breasts but also appearing on the trunk as brownish tinea versicolor and as annular ringworm with central healing

Diagnosis of the Causative Agent The causative agent may usually be suspected from the patient s exposures the time and circumstances of development of the lesions and their distribution It should be remembered that delicate areas of skin are more susceptible If the hands are uniformly exposed to the irritant the skin of the dorsum and between the fingers usually reacts more than the palms Contact dermatitis due to nail polish usually affects the eyelids or neck rarely the hands

The diagnosis may be established by reproducing the lesion with the patch test in which the suspected agent is applied to normal skin of the back arm or thigh covered with a small adhesive dressing and left in place for two or three days Unless the substance is one which is known to be free of primary irritant effects a suitable concentration must be selected by reference to a textbook of dermatology such as that of Sulzberger To avoid excessive reactions the patch test should not be done during the active stage of acute dermatitis and if severe itching develops before the usual period of observation the patch should be removed promptly and the area washed with soap or a suitable solvent

Prognosis and Complications Complete recovery usually occurs within one to three weeks of the last exposure to the cause Sensitization must be expected to persist indefinitely Nephritis has been reported in a few cases as a complication of severe Rhus dermatitis but the etiological relationship is not clearly established

Treatment Most mild cases heal promptly if the causative agent is discovered and removed Local treatment of more severe cases is selected according to the stage of the lesion wet dressings of 5 per cent aluminum acetate for acute oozing lesions and antipruritic lotions such as calamine lotion with phenol for dry lesions Hydrocortisone ointment 1 0 or 2 5 per cent is effective for localized lesions In severe or spreading dermatitis particularly Rhus dermatitis prednisone or prednisolone 5 to 10 mg may be given every six to eight hours until the condition is controlled the dose is then tapered off in the course of a week

When exposure to a known causative agent is unavoidable a protective silicone cream should be applied to the exposed skin before contact and the area scrubbed with soap and water after exposure Patients who have frequent recurrences of Rhus dermatitis despite reasonable precautions to avoid contact should receive preventive desensitization This may be carried out either by injections of an extract of the plant or by oral administration These should not be given during the active stage of the disease Such measures do not confer complete protection but are useful in conjunction with careful avoidance

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Urticaria

Definition Urticaria or hives is an eruption of the skin characterized by transitory sharply demarcated elevated flat topped wheals usually accompanied by erythema and itching This rash may occur without other symptoms or as one manifestation of a systemic disease

Etiology Urticaria may be due to a variety of different causes the relative importance of which varies in different localities and different types of practice

1 Allergy to foods is probably the most frequent cause of acute urticaria but it is relatively less important in chronic cases Shellfish fish nuts berries and other fruits are common offenders but almost any other food may be the cause The urticarial reaction to food may be immediate or delayed for twelve hours or more Skin tests are usually helpful only in the immediate reactions In severe acute cases gastrointestinal and respiratory manifestations of food allergy may also be present

2 Allergy to drugs particularly penicillin is a frequent cause Urticaria due to penicillin frequently is part of a reaction resembling serum sickness with an incubation period of a week or more and lasting another week or two but it may persist for months without further exposure to the drug

3 Biological medications containing protein may produce urticaria either as an immediate allergic reaction or as delayed serum sickness In addition to heterologous antiserum insulin and allergen extracts are common offenders in the immediate type of reaction

4 Allergy to substances touching the skin surface such as silk wool and animal pets is occasionally a cause

5 Infections of the teeth tonsils sinuses and occasionally of other sites are among the commonest causes of chronic urticaria Fink and Gay reported that infection was the cause in 30 per cent of 170 chronic cases

6 Infestation by parasitic worms is an important factor in localities where they are prevalent In susceptible persons scabies lice mosquitoes bedbugs and other biting insects may produce typical urticaria

7 Physical allergy to cold light heat or scratching occasionally is the primary cause More often heat and scratching act as secondary factors in urticaria due to other causes

8 Stress and emotional factors are major causes of chronic urticaria In many instances no other etiology is apparent Sometimes they are secondary factors in cases primarily due to other causes

9 Endocrine factors particularly menstruation menopause and thyroid insufficiency appear to play a part in some cases—whether primary or secondary is not clear

In a large proportion of chronic cases variously estimated from 25 (Fink and Gay) to 90 per cent (Hopkins and Kesten) no cause can be clearly established

The incidence of urticaria is higher in people with a personal or family history of allergies of the familial type but the condition is by no means limited to this group

Pathogenesis The urticarial wheal consists of edema of the skin and results from dilatation of the small vessels and transudation of fluid through the walls of the capillaries in the affected area The reaction is inhibited by adequate doses of antihistamine drugs and similar lesions may be produced in normal skin by the intracutaneous injection of histamine or histamine liberators suggesting that the local release of histamine is a factor in pathogenesis There is some evidence that acetylcholine and other intermediaries may also be involved

In urticaria due to heterologous serum parasitic worms or insect bites and in the immediate urticarial reactions to foods the release of histamine results from an antigen antibody reaction of the immediate allergic type Circulating antibodies are usually present and an urticarial wheal may be produced by a skin test with the antigen In urticaria resulting from infection non protein drugs or delayed allergic reactions to foods such an antibody mechanism is rarely demonstrable but some allergic phenomenon is believed to be involved The mechanism by which stress produces urticarial wheals has not been clearly established

Symptoms The typical lesions are multiple rounded areas 1 to 4 cm in diameter with a sharply defined edge palpably raised above the surrounding skin surface Both the wheal and the surrounding skin are erythematous but if the skin is gently stretched the wheal blanches and stands out clearly The individual lesions usually fade in six to twenty four hours but successive crops may appear in the same or different areas The palms soles and scalp are rarely affected When the eyelids lips

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the hereditary form with abdominal pain and vomiting suggestive of an inflammatory or obstructive disease

Diagnosis The nature of the lesion is generally apparent from the absence of pain and heat and usually of redness The presence of simple urticaria elsewhere on the body is also helpful The underlying structures—for example the teeth and *sinuses in lesions of the face—should* be carefully examined for evidence of infection Edema persisting a week or more without remission is rarely angioneurotic edema In doubtful cases a therapeutic trial with the drugs noted below may be helpful A distinction between the sporadic and the hereditary forms should be made on the basis of the family history because of the difference in prognosis

Prognosis In the hereditary form frequent recurrences and visceral manifestations are expected Death from edema of *the glottis is the most frequent termination* occurring in 21 per cent of 170 cases reviewed by Bullock In the nonhereditary form this complication is rare Periodic recurrences over a period of months or years are common unless the cause is found

Treatment. The response of large swellings to symptomatic medication is slow Epinephrine is indicated particularly if the tongue pharynx or larynx is involved One or two doses of 0 5 ml of the 1 1000 aqueous solution may be followed by 1 0 *ml of the 1 500 suspension in oil intra*muscularly for a prolonged effect Relatively large doses of the antihistamine drugs are required Tripelennamine (Pyribenzamine) or diphenhydramine (Benadryl) 50 to 100 mg may be given every four hours In severe or resistant cases prednisone or prednisolone 10 to 15 mg may be given every six hours until the lesion subsides or corticotropin gel 40 to 80 units injected intramuscularly

When the pharynx or larynx is affected vigorous treatment and close observation are essential Preparations should be made for a prompt tracheotomy if necessary

In recurrent or persistent cases an effort should be made to determine the cause and treatment should be directed at its elimination Infections of the teeth tonsils paranasal sinuses or other organs should be treated appropriately Food allergens suspected as causative factors on the basis of history observation or skin tests should be avoided The role of physical or emotional stress should be carefully evaluated

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Frythemas

The erythemas are a group of skin rashes varying in morphology but all result from reactions of the small blood vessels of the skin They appear most often as manifestations of sensitization in systemic diseases and as evidences of drug allergy but occasionally without determinable cause Their classification in the three groups to be described is based on morphology rather than etiology which is quite similar in all *Urticaria* described in the preceding section and *allergic purpura* described in the section on Hemorrhagic Diseases are closely related phenomena often occurring with the erythemas of this group

TOXIC ERYTHEMA

The commonest type of erythema simple toxic erythema is a diffuse red rash spread symmetrically over the trunk thighs and less often the face and arms This may begin as distinct macules which gradually become confluent (morbilliform rash) or as a diffuse redness which spreads and becomes more intense (scarlatiniform rash) The eruption results from a general dilation of the cutaneous blood vessels of the affected area In severe cases the vascular reaction may result in small purpuric extravasations of the blood into the skin The simple erythema blanches on pressure making apparent the purpuric lesions which do not

Aside from the exanthemata of childhood measles rubella and scarlet fever of which they are a cardinal sign rashes of this type occur in such other infectious diseases as infectious mononucleosis and rat bite fever Morphologically similar rashes both morbilliform and scarlatiniform are common as manifestations of

or genitalia are involved the lesions are less sharply defined and are accompanied by subcutaneous edema producing the picture of angioneurotic edema Itching is usually marked and scratching often produces new lesions of elongated form The total duration of the attack may be a few hours or it may persist for weeks or months

Diagnosis In severe cases one must consider the possibility that the eruption is part of a systemic allergic reaction Simple urticaria should be distinguished from urticaria pigmentosa an infiltration of the skin (and often other tissues) by mast cells in which urticarial wheals subside to leave permanently pigmented brownish macules Differentiation from insect bites is not always easy since allergic persons may react to them with typical urticaria Usually the bite shows a central puncture and as the wheal fades an itching papule persists for a day or more

Treatment Symptomatic relief of acute cases usually may be obtained by the use of epinephrine 1 1000 0 5 ml hypodermically repeated after fifteen to thirty minutes if necessary or ephedrine 25 to 50 mg by mouth Antihistamine drugs such as tripelennamine (Pyribenzamine) 50 to 100 mg diphenhydramine (Benadryl) 50 to 100 mg or chlorprophenpyridamine (Chlor Trimeton) 8 mg every four to six hours are more suitable in prolonged attacks If these drugs are not effective prednisone or prednisolone 5 to 10 mg every six to twelve hours may be used for periods of a week or two Calamine lotion with phenol is helpful as a local application for the relief of itching

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Angioneurotic Edema

Definition *Angioneurotic edema* angioedema or giant urticaria is characterized by transitory localized painless swellings of the subcutaneous tissue or submucosa of various parts of the body It occurs in two forms a rare *hereditary* form in which involvement of the larynx and viscera is frequent and a more common sporadic or *nonhereditary* type in which visceral lesions are less prominent

Etiology The hereditary form shows a strong familial tendency the 181 cases reviewed by Dunlop and Lemon representing only 22 families and 33 being reported in one family In all known marriages in which one parent was affected Phillips and Barrows found that 168 of the offspring developed the disease while 167 did not This ratio suggests a Mendelian dominant character However in 37 marriages in which a grandparent but neither parent had the disease 17 of 111 offspring were affected indicating that a more complex genetic mechanism is involved There is no definite evidence that allergy infection and stress are significant etiological factors in this hereditary type of edema

The nonhereditary or sporadic type is essentially a giant form of urticaria often occurring with simple urticaria and due to similar causes notably allergy to foods or drugs infection and emotional stress This type is more common in people with a personal or family history of allergy but also occurs in others

Pathogenesis The development of angioedema like that of urticaria results from dilatation of the small blood vessels and transudation of fluid through the capillaries but the lesion of angioedema is primarily in the subcutaneous tissue The overlying skin may or may not be affected The vascular change is believed to be due to local release of histamine

Symptoms The lesion is most often single but may be multiple It consists of a tense nonpitting rounded swelling a few centimeters or more in diameter The edema is localized but lacks the sharply defined raised border typical of urticaria The overlying skin is usually normal in color and temperature but may be slightly reddened There is no pain itching is rare and the chief sensation is one of distention The individual lesions persist for one to three days and leave no residual changes Successive attacks may involve the same or different locations The face hands feet and genitalia are the skin areas most often affected Involvement of the lips tongue and pharynx is not unusual In the hereditary form laryngeal edema is a frequent cause of death but this lesion rarely occurs in the sporadic type Involvement of the gastrointestinal system is also common in

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allergy to a wide variety of different drugs notably the sulfonamides thiouracil arsenicals and para aminosalicyclic acid These drug rashes are often but not always accompanied by drug fever of 101° to 104° F If the patient is taking the drug for the first time these two manifestations of drug allergy usually appear simultaneously in the second week of use but in patients previously sensitized they may be apparent in a few hours In general both rash and fever subside promptly when the causative drug is discontinued

ERYTHEMA MULTIFORME

Erythema multiforme is an acute eruption of the skin manifested by various lesions which may include macules papules vesicles bullae urticarial wheals and purpura present simultaneously or at different stages of the eruption The distribution is symmetrical involving the extremities particularly the dorsal surfaces of the hands and feet the face and trunk are less often affected The mucosae of the mouth are frequently involved the penis and vagina occasionally

The onset is abrupt and often accompanied by fever The initial lesions are usually intensely red macules or urticarial wheals In the course of a day or two these lesions may show central clearing to produce ring forms or characteristic target lesions composed of two concentric rings In more severe cases the initial lesions progress rapidly to bullous and purpuric forms Coalescence of individual rounded lesions gives rise to bizarre shapes and sizes The appearance of successive crops of lesions leads to the simultaneous presence of many stages Itching is usually not severe The attack tends to subside completely in a period of a week to a month but recurrences are common

This type of rash may be associated with infections particularly rheumatic fever It is also one of the skin manifestations of serum sickness and of similar reactions to penicillin Other drugs known to produce allergic rashes of this type include sulfonamides phenylbutazone arsenicals and antipyrine Some cases of erythema multiforme are associated with malignant tumors an initial attack in middle age or later should suggest that possibility A considerable proportion of the cases in children recur periodically without known cause

The only effective treatment is with drugs of the cortisone group—for example prednisone or prednisolone 10 to 15 mg every six hours until the condition is controlled

Stevens Johnson Syndrome A severe type of bullous erythema is ectodermosis erosiva pluriorificialis commonly known as Stevens Johnson syndrome which affects children and young adults The onset is characterized by high fever malaise and ulcerative lesions of the conjunctivae mouth genitalia and anus followed in a day or two by a generalized bullous eruption The etiology of this type is unknown Recovery may be followed by permanent damage to the eyes It is not infrequently fatal Cortisone derivatives are the most effective medications Tetracycline or other antimicrobial drugs may be used to control secondary infections

ERYTHEMA NODOSUM

The rash of erythema nodosum consists of a relatively few tender red or purplish nodules usually 2 to 5 cm in diameter appearing chiefly over the shins but occasionally on the thighs and forearms These subside without ulceration over a period of two weeks but successive crops may appear so that the total duration may be four to six weeks There is no itching but pain is frequent The onset is characterized by fever and general malaise Histological sections of the lesions show dilation of the vessels and dense perivascular infiltration of the subcutaneous tissue by wandering cells with some extravasation of red cells This type of rash usually results from allergic reactions to various infective agents and certain drugs It occurs most frequently as a sequela of hemolytic streptococcus tonsillitis or pharyngitis but may also be associated with rheumatic fever tuberculosis coccidioidomycosis ulcerative colitis lymphopathia venereum sarcoidosis and other systemic diseases The drugs most frequently causing this type of reaction are the sulfonamides thiouracil bromides and iodides

Because of the possible implications of serious systemic diseases careful diagnostic studies to establish the cause are warranted in all cases Therapy is directed primarily at the underlying disease Symptomatic treatment of the eruption is only occasionally needed Aspirin is helpful for pain The most effective medications are cortisone derivatives but these should be used only if the possibility of tuberculosis has been excluded

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Diseases of Connective Tissue

Introduction

The collagen or connective tissue diseases represent a group of clinical syndromes which are considered together because they have certain histological features in common such as widespread inflammatory damage in the connective tissue and the production of fibrinoid change in the ground substance Each of these diseases presents a distinct clinical pattern but they are in general characterized by constitutional manifestations as well as local lesions in joints blood vessels heart skin muscle and the supporting reticulum of the internal organs The clinical features are largely determined by the distribution of these lesions and the rate of development of the tissue changes The symptomatic response of certain manifestations of these diseases to adrenocortical steroids stimulated the belief that there might be a common thread running through their etiological background increasing experience *however suggests that the pituitary* adrenocortical system has only a regulatory function damping down reactions to in*jury and disease but having no basic rela*tion to the fundamental factors concerned in pathogenesis

Before discussion of the various diseases in this group it would be well to summarize the current knowledge of the anatomy physiology and pathological physiology of the connective tissue system The supporting system or connective tissue system is the extracellular framework of the body which is composed of structural elements (the fibers) which are largely protein in composition set in a nonstructural matrix (the ground substance) largely polysaccharide in nature For the performance of its supporting and lubricating functions the system combines a *maximal* degree of physical stability with a minimal metabolic activity

The principal cellular element is the fibroblast which along with its close relatives the osteoblast and the chondroblast seems to be responsible for the elaboration of most of the other endogenous elements and for their maintenance Other cellular elements include the mast cell concerned in the formation of heparin and the wandering cells or macrophages In fresh granulation tissue the cells are relatively numerous and the intercellular material is scanty and largely mucoid in nature In well differentiated adult tissues the cells are relatively few inactive and tend to be separated from each other by large amounts of intercellular material

The fibrous constituents of connective tissue comprise two main groups collagenous and elastic Collagen is a fibrous protein occurring in wavy *birefringent* bundles of unbranched acidophilic fibrils cemented together in a polysaccharide ma*trix and characterized chemically by low* content of aromatic amino acids and high content of proline hydroxyproline and *glycine It represents approximately* 30 per cent of the total body protein Nageotte and others demonstrated that certain collagens such as the rat tail tendon could be dissolved in dilute acids to form clear viscous solutions Fibers could be reprecipitated from such solutions by the addition of sodium chloride This phenomenon has been interpreted as a simplified model for the biological fibrogenesis of collagen The structural specificity of the fibers formed resides in the dissolved collagen structures precipitated from the solution These and *other studies have led to the concept of* a fundamental collagen building block termed tropocollagen which is manufac*tured and released in soluble* form by the

cell After extrusion into the extracellular environment ionic and other conditions favor its precipitation and orderly lineal aggregation into the collagen fibril The argyrophilic reticular fibers believed to be precursors of collagen fibrils are arranged in parallel wavy bundles Such fibers form the delicate supporting network of organs like the spleen They are also found in developing connective tissue and are the finest of the three types Though distinguishable from collagenous fibers by their staining reaction they are made up of the same macromolecular fibrils the reticulin fibers simply representing smaller aggregations of fibrils Elastic fibers are characteristically branched and smooth They are found in large numbers only in special areas such as ligaments and the walls of arteries

Histologically the mucoid forms the ground substance which lies between the connective tissue fibers and fibrils It may show metachromasia with toluidine blue and may stain deeply with the McManus technique Chemically it is composed of mucopolysaccharides which are highly polymerized long chain forms of a basic disaccharide composed of equimolecular parts of glucuronic acid and an amino sugar These mucopolysaccharides are divided into two groups on the basis of the presence or absence of sulfate Sulfate free hyaluronic acids are concentrated in ground substance between the formed elements and appear to function mainly as lubricants and shock absorbers Sulfated polysaccharides form cement substance within collagen and cartilage and also function as polyelectrolytes in the binding of cations in a manner comparable to that of the synthetic ion exchange resins In the tissues the polysaccharides are normally highly polymerized and the increased spread of fluid which follows the introduction of hyaluronidase containing extracts has been attributed to depolymerization of the tissue polysaccharide The capacity of polysaccharides to form viscous lubricating fluids or a stabilizing tissue matrix depends upon their degree of polymerization rather than upon the total content Polymerization is greatest at the site of formation of basement membrane Where toughness is a characteristic sulfate mucopolysaccharide is present acting as a cementing material between the collagen bundles Where lubrication is the prime need as in joint spaces and the vitreous of the eye hyaluronic acid is found

Physiologically the complex functions in connective tissue depend for their integrity not only on fibroblastic activity but also upon a satisfactory supply of building material from blood and important regulators including enzymes vitamins and hormones The hyaluronidases antihyaluronidases collagenases and heparin are examples of enzymes and enzyme inhibitors playing an important role among the vitamins and hormones are ascorbic acid testosterone estrogen and adrenocortical steroids All the factors and pathways have not been delineated but the system is clearly a "connecting substance forming a barrier which must be crossed by water electrolytes nutrients and metabolites being exchanged between blood and the parenchymal cells in all areas

There are three principal reactions of connective tissue to injury fibrinoid necrosis fibrillary augmentation leading to sclerosis and cellular invasion and proliferation Following trauma or inflammation a tissue substance is released which causes an increase in capillary permeability with influx of polymorphonuclear leukocytes lymphocytes and monocytes At the area of increased permeability there is local adhesion of leukocytes to the capillary wall In the development of sclerosis or fibroplasia new fibroblasts soon appear and shortly afterwards ground substance As reticular and collagenous fibers develop new blood vessels grow out from capillary buds on pre-existing vessels

Cortisone and other similar adrenal steroids decelerate and thereby inhibit fibroplasia Desoxycorticosterone acetate and growth hormones accelerate and augment it The spreading reaction induced by hyaluronidase is inhibited by ACTH Cortisone may also modify the invasive tendency of macrophages through an effect on capillary permeability and margination of the white cells

In the absence of vitamin C fibroblasts migrate widely multiply rapidly assume the morphology of embryonal connective tissue and produce a liquid material instead of normal matrix No new collagen is laid down and reticulum does not appear Thus the fibroblast matures but fails to produce the normal extracellular components of connective tissue

With advancing age the mucoid content of most connective tissues decreases while the collagenous component increases and tends to be organized into a coarser fiber pattern These tissues become less elastic and resilient and as a result less able to resist mechanical forces This is one rea

son why our limbs become stiff and readily damaged by trauma as aging occurs

Fibrinoid degeneration along with the accompanying inflammatory reaction has come to be the accepted histological hall mark of the collagen diseases In the fibrinoid lesion connective tissue cells are either few or absent and the regular fiber pattern of normal connective tissue is re placed by swollen indistinct bundles or clumps of amorphous material which stain more intensely with eosin than the sur rounding connective tissue In sections treated by the McManus technique the fibrinoid areas stain strongly with the ma genta color considered to indicate the presence of polysaccharides Fibrinoid differs markedly from normal collagen and the opinion has been expressed that in its formation the collagen polysaccharide com plex of normal connective tissue is de stroyed the collagen being removed but the polysaccharides remaining in an un usually insoluble form

As our knowledge of the connective tis sue system and its normal function in creases and the various clinical and patho logical syndromes are more clearly delineated investigative developments in regard to etiology and pathogenesis will emerge on which sound and specific meas ures for prevention and treatment can be based The clinician who studies these prob lems should develop the habit of regarding the connective tissue system as a whole if the diverse body of information which is accumulating is to be efficiently and use fully synthesized

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Systemic Lupus Erythematosus

Introduction and Definition Systemic lupus erythematosus (SLE) is a disease with varied clinical manifestations asso ciated with lesions of connective tissue in the vascular system the dermis and the serous and synovial membranes There is usually a prolonged clinical course charac terized by exacerbations and remissions over a period of years The development of the typical erythematous butterfly facial lesion facilitates diagnosis but is often not present Frequently there are marked con stitutional symptoms and the multitude of visceral manifestations may present in a complex pattern making diagnosis difficult

Classification into acute subacute and chronic categories other than to describe the clinical course of dermal lesions serves no purpose The activity of the disease varies and the acuteness of the illness merely denotes the severity at any one time The term SLE refers to the generalized form of the disease and the terms discoid and dis seminated are used to describe the dermal lesions

Incidence With the recognition that SLE is usually a chronic relapsing process with protean manifestations it is clear that it is relatively common particularly among young females Several observers in gen eral hospitals have collected 100 to 200 cases since the advent of the L E cell test as a diagnostic aid However until a spe cific universally positive diagnostic test is developed the true incidence will remain unknown

Etiology Infectious agents both viral and bacterial have been implicated but on no solid evidence The predominance in fe males has led to speculation about endo crinological factors Some constitutional predisposition of unknown character seems possible Because of the multitude of pro tein abnormalities observed this disease might be due to an auto immune mecha nism

Pathology and Pathogenesis There may be a paucity of anatomical findings even though the patient has an active fulminat ing disease Microscopically the lesions in the connective tissue include (1) fibrinoid change (see Introduction) (2) sclerosis of collagen as manifested by periarterial fibrosis in the spleen (3) the development of hematoxylin bodies and (4) cellular infiltration The so called hematoxylin bodies are purple staining globules which arise from alteration in the nuclei of cells of mesenchymal origin They have been noted in the heart lymph nodes kidney lung and spleen The composition of the nucleoprotein of these bodies differs from that of normal nuclear material in the ab sence of histone some loss of deoxyribo nucleic acid (DNA) and in the seemingly increased amount of unusual protein ma

terial The most recent evidence does not support the concept that there is depolymerization of DNA

Clinical Manifestations At onset a single organ system may be involved or dysfunction may be noted in several systems Initially the skin and joints are most frequently affected but the disease may begin with a pneumonitis thrombocytopenic purpura or a psychotic episode suggesting a local rather than a generalized process The initial symptoms may be vague making it difficult to date the onset The patient may state that she "has always been sensitive to the sun" or has had recurrent mild arthralgia for many years The majority of patients have constitutional difficulties with fever

Joint Involvement Most commonly involved are the hands wrists elbows shoulders knees and ankles Characteristically there is a disproportion between the severity of the discomfort and the objective evidence of arthritis Joint pains tend to appear episodically and are often migratory In some patients contractures muscular atrophy and joint deformity may be disabling Tenderness in muscles and periarticular tissues frequently accompanies the arthritis The muscle involvement may be so extensive as to suggest dermatomyositis or a primary myopathy

Mucocutaneous Manifestations The typical "butterfly" eruption appears in less than half the patients and in a significant number cutaneous lesions do not develop Symmetrically distributed erythematous lesions may be seen on the ears neck back chest shoulders arms hands and feet The other characteristic but rare dermal lesion is purplish erythema often followed by ulceration and scarring about the nail beds Urticaria and angioneurotic edema are frequent The pigmentation and thickening of the skin may resemble scleroderma Subcutaneous nodules have been described Vascularization of the cutaneous lesions may occur with the development of telangiectases The mucosal lesions are erythematous petechial or ulcerative

The dermal lesions in chronic discoid lupus consist of erythematous plaques of varying sizes with scaling and follicular plugging followed in the healing stages by atrophy and scarring with either hyperpigmentation or areas of vitiligo In the localized form the lesions are confined to the face ears and scalp while in the generalized form also referred to as the chronic disseminated form lesions appear elsewhere on the body The patient with the chronic discoid form may suddenly develop acute systemic manifestations or such manifestations may be present in variable and less fulminating form over many years

Renal Involvement Kidney involvement is present in 75 per cent of patients dying of SLE Serial biopsies reveal that the earliest renal lesion is a localized membranous glomerulitis With progression there is the appearance or increase of fibrinoid material in the basement membrane adhesions develop between the tuft and Bowman s capsule and in some cases local areas of necrosis are found Tubular degeneration is usually evident In the end the kidney may be indistinguishable from that of early chronic glomerulonephritis of the common type

The renal disease may run a fulminating course (pseudonephrotic syndrome) in which glomeruli are severely damaged from the onset with death from kidney failure within a few weeks or months The clinical picture is that of nephrosis with the exception that the serum cholesterol is low

On the other hand it may develop slowly in a patient ill for a long period with other symptoms In the early stage the urine may contain protein leukocytes in clumps and leukocyte casts leading to an erroneous diagnosis of pyelonephritis As the lesion progresses erythrocytes and granular casts appear in the urine of most patients and epithelial cells fatty casts and oval fat bodies in the urine of some patients The clinical manifestations include nocturia polyuria and thirst Many patients pass through an edematous stage associated with hypoalbuminemia hypercholesterolemia and massive proteinuria Histologically membranous and proliferative changes are seen in the glomerular tufts and tubular degeneration is usually evident When this nephrotic syndrome appears other clinical manifestations may be quiescent and the diagnosis of SLE overlooked The edematous stage may persist for months gradually progressing into one of chronic renal insufficiency Secondary infection of the genitourinary tract is common

Cardiovascular Manifestations Over half the patients have involvement of the pericardium endocardium or myocardium Pericarditis is usually manifested by precordial discomfort or a friction rub significant degrees of effusion being unusual In a disease characterized by fever and anemia the interpretation of systolic murmurs is difficult and the correlation of clinical and pathological evidence of the

verrucous endocarditis of Libman Sacks is not good Occasionally a superimposed bacterial endocarditis develops usually on the mitral valve where the verrucous lesions are most common At times lesions in the myocardium result in heart failure with tachycardia gallop rhythm and cardiac enlargement Raynaud s phenomenon is often an early manifestation

Pleural and Pulmonary Involvement Pleurisy is one of the hallmarks of SLE An anaphylactoid pneumonitis is frequently present and may resemble atypical pneumonia of viral origin There may be progressive tachypnea dyspnea and cyanosis Scattered fine or coarse rales usually at the lung bases may be the only findings Radiological study may reveal elevation and fixation of one or both diaphragms with areas of platelike atelectasis above Bacterial infections of the lungs are common

Nervous System Manifestations Over one fourth of these patients show evidence of mental and neurological dysfunction The mental reactions are diverse and include anxiety memory defects hallucinations and obsessional and paranoid reactions Convulsions are frequent Other neurological findings described are diplopia nystagmus hemiplegia and polyneuritis The spinal fluid may show increased cells and protein sometimes accompanied by signs of meningitis Cotton wool retinal exudates are frequently observed In the absence of hypertension and diabetes these cytoid bodies in the nerve fiber layer of the retina are a helpful point in diagnosis

Gastrointestinal Manifestations These include anorexia nausea vomiting and abdominal pain which may be so acute as to simulate conditions requiring surgical intervention Dysphagia is due to arteritic lesions in the esophagus Pancreatitis has occasionally been prominent Diarrhea with bloody stools and abdominal cramps may be present and severe paralytic ileus has been noted

Liver Spleen and Lymph Nodes Although hepatomegaly is often found the usual cause is fatty infiltration and the lesions of lupus are seldom present The spleen is palpable in 15 to 20 per cent of cases Regional or generalized lymph node enlargement occurs in over half the patients and may be so impressive that a diagnosis of a primary lymphatic disease is made

Hematological Abnormalities Leukopenia is common and is due to a predominant decrease in mononuclear cells with a high proportion of neutrophils Eosinophils are often reduced in number Leukocytosis is unusual unless the process is fulminating but may result from superimposed infection or steroid therapy

Purpura is usually the result of a vascular defect Occasionally a hemorrhagic disorder similar to idiopathic thrombocytopenic purpura may develop preceding by months or years other obvious manifestations of SLE ACTH or adrenocortical steroids usually produce a transient rise in platelets Splenectomy has been uniformly effective in the writer s experience and in most instances there has been no recurrence

In the majority of cases an anemia due to retarded erythropoiesis develops If there is renal insufficiency or a superimposed infection it may become severe A few patients have an acute hemolytic anemia which has the character of an acquired auto immune disorder with reticulocytosis jaundice and a positive Coombs test Splenectomy is of no benefit but adrenal steroids are effective in controlling the hemolysis

Hypergammaglobulinemia is demonstrable in most cases and other protein abnormalities including increase in fibrinogen autoagglutination of erythrocytes elevation of the sedimentation rate positive flocculation tests and biological false positive tests for syphilis are frequently encountered Cryoglobulins have been noted as well as the occasional appearance of a circulating anticoagulant associated with prolongation of clotting and prothrombin times

L E Cell Phenomenon A protein factor contained in the plasma of the majority of cases can induce formation of L E cells in leukocytes obtained from blood marrow or other sources

The typical L E cell consists of a neutrophilic granulocyte distended by a large purple red homogenous globular inclusion body which compresses the nucleus against the cell membrane leaving only a thin rim of cytoplasm The inclusion body is derived from nuclear material released from other leukocytes and altered under the influence of the plasma factor The L E cell is then formed when this altered nuclear material is ingested by a phagocytic cell In positive L E cell preparations there are frequently extracellular masses of globular material identical in appearance and staining reaction with the L E cell inclusion This extracellular material is often surrounded by polymorphonuclear leukocytes forming rosettes

Heparin is the preferable anticoagulant because there is less distortion of the leukocytes Coagulation and rotation with glass beads result in injury to leukocytes thus presenting more nuclear material for interaction with the L E factor in serum

Recent studies have shown that when nuclear material is incubated with positive L E serum and then the nuclei removed by centrifugation the serum loses its ability to induce L E cell formation If all the DNA is removed from the nuclear material by treatment with DNA ase no L E factor is absorbed Absorption of L E factor was also prevented by prior treatment with protamine thought to bind the phosphate group of DNA and with Atabrine an agent having some therapeutic action in this disease When slides containing L E cells are reacted with fluorescent rabbit antiserum to normal human gamma globulin nuclei undergoing change preliminary to phagocytosis during L E cell formation and the inclusion bodies of L E cells fluoresce brilliantly indicating localization of the gamma globulin presumably the L E factor on the affected nuclei These findings suggest that the L E serum factor has an affinity for nuclear nucleoprotein and that DNA is involved in the bond The question may be raised as to whether the L E factor could be an auto antibody to nucleoprotein or deoxyribonucleic acid There is no regular correlation between the severity of the disease and the number of L E cells produced Some patients with unequivocal SLE in an active stage cannot be demonstrated to form L E cells

Leukocytes which have engulfed lymphocyte nuclei have been mistaken for L E cells False positive results have been reported in cases of rheumatoid arthritis hemolytic anemia and glomerulonephritis but it seems probable that the patient s disorder was a manifestation of SLE Patients may develop a lupus like syndrome after prolonged therapy with hydralazine and in some of these cases L E cells have been demonstrable The reported rare occurrence of L E cells with other drug reactions particularly penicillin hypersensitivity remains to be clarified

L E cells have been found occasionally in patients with a syndrome referred to as active chronic hepatitis the features of which are prolonged jaundice occurrence in young females pyrexial episodes hepatomegaly and pronounced splenomegaly occasional ascites and a raised gamma globulin level Histologically there are fibrosis and nodular regeneration with striking infiltration of lymphocytes plasma cells and histiocytes A butterfly rash has been noted and also hemolytic anemia It is postulated that viral and possibly nutritional damage to the liver can lead to a situation in which liver-cell components become antigenic and may stimulate the production of antibodies which react damagingly with liver and other body tissues leading to perpetuation of the hepatitis and occasionally to the initiation of the clinical picture of lupus erythematosus

Course of SLE The course of SLE is characterized by periods of exacerbation and remission during which a number of organ systems may be involved in an episodic manner The disease may extend over many years or may end in a fulminant manner in a few weeks or months A protracted course during which the various manifestations become evident in a confusing and complicated manner is the usual picture Spontaneous remissions are common and may occur on more than one occasion lasting for months or even years The development of an infection or the administration of a drug may serve as the trigger for enhancement of activity

Before the antibiotic era patients most frequently died of a complicating infection particularly of the respiratory or urinary tract but now progressive renal involvement or central nervous system disturbances due to the disease itself are the most ominous developments

There is a sustained false positive serological test for syphilis (BFP) in approximately 20 per cent of patients with SLE Pertinent to the clinical course of SLE is the etiological background of the chronic BFP phenomenon One hundred forty eight patients all essentially well when shown to have this phenomenon have been followed from one to twenty years Approximately 7 per cent have subsequently developed verified SLE 5 per cent typical rheumatoid arthritis and 30 per cent one or more clinical episodes compatible with a widely disseminated connective tissue disorder In another 29 per cent still clinically well other serum protein abnormalities have been discovered

Considering the cases of SLE which can be clinically recognized and estimating survival from time of diagnosis one may expect a mortality of about 10 per cent per year Survival may be much longer if one estimates duration from retrospective determination of the first manifestation of the disease

Diagnosis The clinical diagnosis of SLE

verrucous endocarditis of Libman Sacks is not good Occasionally a superimposed bacterial endocarditis develops usually on the mitral valve where the verrucous lesions are most common At times lesions in the myocardium result in heart failure with tachycardia gallop rhythm and cardiac enlargement Raynaud s phenomenon is often an early manifestation

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Hypergammaglobulinemia is demonstrable in most cases and other protein abnormalities including increase in fibrinogen autoagglutination of erythrocytes elevation of the sedimentation rate positive flocculation tests and biological false positive tests for syphilis are frequently encountered Cryoglobulins have been noted as well as the occasional appearance of a circulating anticoagulant associated with prolongation of clotting and prothrombin times

L E Cell Phenomenon A protein factor contained in the plasma of the majority of cases can induce formation of L E cells in leukocytes obtained from blood marrow or other sources

The typical L E cell consists of a neutrophilic granulocyte distended by a large purple red homogenous globular inclusion body which compresses the nucleus against the cell membrane leaving only a thin rim of cytoplasm The inclusion body is derived from nuclear material released from other leukocytes and altered under the influence of the plasma factor The L E cell is then formed when this altered nuclear material is ingested by a phagocytic cell In positive L E cell preparations there are frequently extracellular masses of globular material identical in appearance and staining reaction with the L E cell inclusion This extra cellular material is often surrounded by polymorphonuclear leukocytes forming "rosettes "

regard in patients with cardiovascular or renal involvement If there is any evidence of tuberculosis adequate antimicrobial therapy should be given during steroid administration

The steroid of choice is administered in the amount necessary to control the active manifestations of the disease and in some patients the manifestations of Cushing's syndrome will result

A majority of patients will be benefited dramatically within a few days General well being is enhanced appetite increases pyrexia is suppressed regression of active cutaneous lesions takes place joint manifestations subside cardiac symptoms decrease unless accompanied by renal involvement and there is usually subjective improvement in those with pulmonary involvement

The initial dosage is maintained for several days If there is no beneficial response the dose is then raised in a stepwise manner until a favorable effect is obtained or indications of overdosage appear The optimum amount for improvement is then maintained until the major signs and symptoms have been suppressed to maximum degree The dose is then reduced in a stepwise manner for example 25 to 50 mg of cortisone every two to four days If there is a recrudescence the dose is again raised On the other hand if there is no exacerbation or if symptoms return to only a minor degree reduction of steroid may proceed The decision to begin lowering the dose of steroid is based more on the status of the clinical manifestations of the disease than on any laboratory observations These hormones merely reduce the inflammatory response and do not affect the fundamental cause of the lesions When the underlying process improves spontaneously little or no steroid therapy will be necessary to keep the patient in a state of clinical remission

When the nephrotic syndrome is present high protein feeding (1 5 gm /kg /24 hours) and dietary sodium restriction are indicated When chronic renal failure is present the dietary protein is restricted to about 40 gm daily The patient should be instructed to maintain an adequate fluid intake (2500 to 3000 ml daily) Frequent electrolyte determinations enable one to anticipate and treat serious electrolyte imbalance The general measures are those used in the management of any patient with chronic nephritis and renal insufficiency No evidence of regression of structural damage has been found to take place during steroid therapy (renal biopsy studies) and neither is there evidence that these hormones cause progression of the renal lesions The patient should be treated with steroids at the earliest sign of renal involvement in the hope of retarding progress or preventing irreversible damage If after steroid administration there is no improvement in the face of serious renal involvement nitrogen mustard may be tried in a single dose of 20 mg intravenously (adults)

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Dermatomyositis

(*Neuromyositis Polymyositis Dermatomucosomyositis Poikilodermatomyositis*)

Definition There has been no more satisfactory definition of this disease in its classic form than that proposed by Steiner An acute subacute or chronic disease of unknown origin characterized by a gradual onset with vague and indefinite prodromata followed by edema dermatitis and multiple muscle inflammation The common denominator of this syndrome is the acute or subacute degeneration of skeletal muscles and the descriptive terms are utilized to indicate the combination of tissues involved in the individual case

Etiology and Incidence The etiology is unknown Many cases have had their onset during or after some type of infection but no causative relationship has been established Other observers have suggested an allergic background a disturbance in vitamin E metabolism or an endocrine factor but no conclusions can be reached from the information available In about 18 per cent

can be made consistently only when the observer appreciates that this syndrome frequently has a protracted course unfolding in an episodic manner over many years When confronted by what appears to be a disorder of a single organ system such as *arthritis a hemolytic anemia* an obscure nephritis or an unexplained psychotic reaction the observer must search the background for past illnesses which might be related SLE may appear with a confusing array of manifestations resulting from multi system involvement in which it is difficult to detect any obvious continuity It is particularly important to look for the variety of plasma protein serological and hematological abnormalities which have been pointed out The diagnosis can often be substantiated by demonstration of the L E cell phenomenon or the proper interpretation of biopsy material obtained from the skin subcutaneous tissues muscle lymph node or kidney

Hydralazine Syndrome Hydralazine is used in the treatment of hypertension In 7 to 10 per cent of patients who receive an average daily dose of 600 mg or more over periods averaging twelve months a syndrome develops which may simulate SLE *It usually appears as the diastolic pressure* falls to normal and is often precipitated by an intercurrent infection Initially there may be chills and migratory joint and muscle pains If the drug is continued a febrile phase ensues manifested by fever pleural pericardial and joint effusions skin sensitivity to light erythematous eruptions *lymphadenopathy and splenomegaly* There may be decreased serum albumin concentration increase in alpha and gamma globulins increased erythrocyte sedimentation rate transient false positive tests for syphilis anemia leukopenia and in some instances the development of the L E cell phenomenon Renal abnormalities are unusual The syndrome is predominant in males and is reversible when the drug is stopped The relationship to total dose and duration of administration does not suggest a sensitization phenomenon

Treatment The control of pain by use of suitable analgesics the treatment of complicating infections with appropriate antibiotics transfusions *for the correction of* anemia and digitalis and sodium restriction in the cases with heart failure are examples of numerous standard measures which are utilized when *indicated* Limitation of activity during the active phase of the disease is desirable Undue exposure to the sun is unwise in view of the frequent presence of photosensitivity and no drugs should be administered unless there is an *urgent therapeutic indication since fulminating* manifestations may be precipitated When fever and joint symptoms are prominent salicylate administration may be beneficial and occasionally the results are dramatic

Certain antimalarial drugs particularly Atabrine and chloroquine are used to treat milder forms of the disease and those patients who have been on high doses of adrenocortical steroids for prolonged periods and in whom it is not possible to reduce the maintenance dose After a period of weeks on these drugs a lichenoid dermatitis may develop or the drug may have to be discontinued because of convulsions a psychotic reaction or gastrointestinal symptoms The most striking result is improvement in the arthritic and cutaneous lesions The suggested dose of Atabrine is 100 mg three times daily after meals If there is no improvement in one week it may be gradually increased to 600 mg daily Larger doses are usually no more effective and the incidence of toxic effects increases Chloroquine is now more often used than Atabrine and appears to be less toxic The effective *dose appears to be about 500 mg* to 750 mg daily This is used for one to four weeks until a clear response is obtained when the dose is reduced to 500 to 250 mg and maintained *In 50 to 75 per cent of patients* there is either clearing of the dermatitis or definite improvement The recurrence rate after stopping the drug is high In view of *the reported cases of severe bone marrow* damage these drugs should be used with caution

The active manifestations of SLE can be most *adequately* and *promptly* controlled by adrenocortical steroid therapy In the moderately or seriously ill patient the starting dose may be cortisone 300 mg hydrocortisone 200 to 250 mg or prednisone 40 to 60 mg There has been little difficulty with permanent adrenal suppression from long term use of these steroids if they are tapered gradually and their administration is not terminated rapidly without prior administration of ACTH With long term use of any of these steroids it is necessary to *employ anticholinergic drugs* antacids and frequent feedings because of the tendency to peptic ulceration The status of carbohydrate metabolism should be followed closely Sodium restriction and oral potassium administration should be employed when moderate or large doses of steroid are given Special care must be taken in this

erythematosus there may be a relation between the appearance or intensity of the cutaneous manifestations and exposure to sunlight In some cases there is extensive calcification in the subcutaneous tissues

An intermittent fever may be present Malaise anorexia and loss of weight are common Involvement of the joints is rarely seen although pain in periarticular areas often results from lesions of the soft tissues and tendons Alopecia of varying degree may develop and hypertrichosis is sometimes noted Occasionally present are lymphadenopathy splenomegaly paresthesias and hemorrhagic phenomena

A mild anemia is often recorded Leukocytosis is infrequent but in some cases there may be an increase in eosinophils lymphocytes or monocytes Creatinuria is a constant finding when there is moderate or severe muscle involvement Other laboratory abnormalities which have been recorded include increase in serum globulin proteinuria hematuria and reduction in serum albumin

The *course* is a progressive one to death in about half of the cases However there may be remissions and exacerbations of activity of the disease The terminal event may be respiratory insufficiency cardiac failure or a complicating infection It would appear that the majority of the patients who survive the first year may enter a very long period in which the process may become quiescent or remain mildly active

Diagnosis When the classic features described are present they are usually sufficient when combined with muscle biopsy to make the diagnosis with certainty Early in the course it may be difficult to distinguish this disease from the edematous stage of scleroderma or scleredema Periorbital edema and muscle tenderness may mimic trichinosis and in other cases there may be a resemblance to polyneuritis myasthenia gravis muscular dystrophy pseudobulbar palsy thyrotoxic myopathy Addison s disease and periarteritis nodosa In the acute form there may be symptoms similar to those of systemic lupus erythematosus such as facial erythema vague arthralgias fever and weakness and sensitivity to sunlight However there are usually distinguishing features There are transitional cases in which the clinical picture has seemed to fit one disease well only to have at a later stage the typical histological picture of the other For example the atrophic dermal changes of scleroderma may be seen in patients with systemic lupus erythematosus or dermatomyositis and in advanced scleroderma there may be extensive muscular involvement However the associated findings the laboratory examinations and the histological picture usually serve to make the diagnosis clear

Treatment Symptomatic treatment should include rest in bed suitable physiotherapeutic measures and special exercises to minimize contractures Salicylates may be helpful in the relief of pain and tenderness but in the acute phase more potent analgesics may be necessary In the early stages when activity of the process is evident corticotropin prednisone and cortisone may produce dramatic relief but large doses sufficient to produce the recognized features of Cushing s syndrome may be necessary over a period of several weeks Striking objective improvement in muscle power may be brought about and sustained with maintenance therapy A few patients have remained in remission when the dose of hormone was gradually reduced and then treatment discontinued after a period of several months When advanced atrophy and fibrosis have developed there is no return of function after hormone administration

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Polyarteritis

(Periarteritis Nodosa Polyarteritis Nodosa Necrotizing Angiitis)

Definition Kussmaul and Maier introduced the term periarteritis nodosa in 1866 to describe a systemic disease characterized by visible nodules along the course of the medium sized muscular arteries The lesions

of the cases of dermatomyositis there is an associated neoplasm of some type such as carcinoma of the breast stomach ovary or kidney Such dermatomyositis is usually acute and is said to be potentially reversible with successful treatment of the neoplasm It has been suggested that the disease is due to development of antibodies against the neoplasm which cross react with other tissue antigens

As evidence of the infrequency of this syndrome only 38 proved cases have been observed in the Johns Hopkins Hospital since 1933 The youngest patient was two and the oldest seventy six at the time of onset the largest incidence being in the fifth decade There was no sex predominance and three of the patients were Negroes

Pathology Histologically the skin may reveal vacuolation of the epithelium perivascular lymphocytic infiltrations atrophy of the epidermis flattening of the rete pegs and edema or fibrosis of the cutis These changes are not specific for this disease The affected muscles may appear swollen and pale in color and have a firm consistency The primary process is one of degeneration of muscle fibers but there may be a variable degree of inflammatory reaction The sarcolemmal nuclei of altered fibers may be increased and vacuolization granular degeneration and fragmentation can be seen in many fibers Perivascular accumulations of mononuclear cells may be present In the acute stage there is active phagocytosis of involved fibers and hemorrhages may occur leading to the use of the term 'hemorrhagic myositis' In the chronic form one sees vacuolated fibers which contain shrunken sarcolemmal nuclei and there is an increase in the endomysial collagen Microscopic changes similar to those seen in skeletal muscle have been observed in the myocardium

Clinical Features and Natural History of the Syndrome Some observers have differentiated cases into two clinical types (1) acute dermatomyositis which is more commonly seen in children and is characterized by an erythematous eruption edema tenderness swelling and weakness of the proximal muscles of the extremities fever and leukocytosis Involvement of the respiratory muscles may lead to a fatal termination but the process may have a self limited course (2) chronic polymyositis which runs a more chronic course begins in the peripheral limb muscles and is not associated with dermal involvement However there are all gradations between these two extremes and cases which begin acutely with erythema and edema of the skin and extensive muscle involvement may pass into the chronic stage with atrophy and fibrosis The dermal and muscular involvement do not always parallel one another and there may be an interval of many months between the appearance of the cutaneous lesions and the evidence of muscle dysfunction

The disease often begins with muscle tenderness followed by weakness and the appearance of cutaneous signs Raynaud's phenomenon may be an early manifestation The muscular involvement is not constant in its distribution and may be limited to one group such as the shoulder or pelvic girdle or may be generalized from the onset in which event the course is usually a fulminating one The element of pain and tenderness seems to depend on the degree of edematous change and may be very intense slight or even absent The muscles may at first feel doughy later become firm and finally show extensive wasting Stiffness and weakness are usually complained of early and are often symmetrical in distribution Later there is marked atrophy and fixation of joints may occur Striated muscles in areas other than the limbs and trunk may be involved giving rise to such symptoms as diplopia dysphagia difficulty in respiration facial weakness and impairment of sphincter control Heart failure may occasionally be present owing to similar changes in the cardiac muscle

The areas most frequently involved by the mucocutaneous lesions are the face eyelids ears buccal mucosa V area of the neck and the skin overlying articulations The eyelids may be swollen and have a characteristic heliotrope coloration due to the presence of small telangiectases Important are the symmetrical cutaneous lesions overlying the small joints of the hands which may show edema a violaceous hue and telangiectases Similar changes may be seen about the larger joints and when scaling is prominent may resemble psoriasis As the lesions regress pigmentation may develop in some cases this may be so widespread as to resemble Addisonian discoloration Cutaneous alterations may be present which resemble the changes seen in scleroderma When there is extensive involvement lesions in various stages of development from acute erythema and edema to atrophy and pigmentation may be observed Subjective symptoms such as pruritus are usually absent As in lupus

affected vessels may show intimal proliferation leading to thrombosis and arterial obstruction with infarct formation The artery may become distended into an aneurysmal saccule and may even rupture In some instances the vascular changes may be limited to the vessels of one system or to a few isolated organs with the result that no single clinical finding is invariably present The lesions may be seen in all stages in any given case from acute ones to those which are completely healed

In hypersensitivity angiitis according to Zeek the smallest branches of blood vessels both arterial and venous are involved and the intense cellular reaction contains many eosinophils The lesions in the individual case are the same age and no chronic or healed lesions are noted

Clinical Features and Natural History of the Syndrome The widespread nature of the vascular lesions reflects itself in symptoms and signs so variable and so often superficially unrelated that no standard clinical description can amply relate the polymorphic manifestations of these illnesses In cases of periarteritis nodosa the general clinical picture presented may be that of (1) a nonspecific subacute or chronic pyrexial illness (2) an atypical abdominal illness (3) a primary renal disease or (4) a combination of polyneuritis and polymyositic manifestations In the accompanying table are listed the principal signs and symptoms as recorded in several hundred reported cases Fever occurs at some time during the course of the disease in almost every case Approximately half of the patients describe a sudden onset accompanied by fever The kidneys are frequently involved albuminuria and hematuria being common findings Hypertension occurs in over half the cases According to Rose and

Symptoms and Signs of Periarteritis Nodosa With Frequency of Occurrence in 300 Cases

	%		%
Fever	85	Jaundice	10
Abdominal pain	65	Convulsions	10
Hypertension	60	Eruptions	10
Edema	50	Diarrhea	10
Neuritis	50	Muscle soreness	10
Weakness	45	Leukocytosis	80
Weight loss	45	Albuminuria	60
Cough and dyspnea	40	Hematuria	40
Vomiting	30	Eosinophilia	25
Headache	30	Uremia	15
Precordial pain	25		

Spencer the blood pressure does not rise until after the appearance of proteinuria or hematuria The elevation seems to be a sequel of renal polyarteritis or glomerulitis but it develops only during the healing stages of these lesions Thus in contrast to the views of Knowles and Blankenhorn the hypertension is not a precursor of the disease but usually is a result of it The recognition of hypertension as a complication of polyarteritis is important as it may be the presenting clinical feature and this syndrome should be suspected in all cases of severe or rapidly progressive high blood pressure associated with fever leukocytosis or unexplained lesions in other systems

The frequency with which the characteristic arterial lesions of periarteritis nodosa are found in one or more of the abdominal viscera or the intestinal tract accounts for the common occurrence of abdominal pain which is often violent and maximal in the umbilical region or in the gallbladder area Anorexia nausea vomiting and bloody diarrhea have been observed and thrombosis of mesenteric arteries may lead to infarction of the bowel Such arteritic lesions may involve the appendiceal pancreatic and hepatic vessels as well resulting in a clinical picture simulating appendicitis hemorrhagic pancreatitis or hepatic necrosis Mucosal ulceration with hemorrhage and perforation has been reported frequently

A painful peripheral neuritis usually bilateral and often asymmetrical is a common finding particularly in the lower limbs Many other signs and symptoms due to arteritic lesions in the nervous system have been noted including meningeal irritation due to subarachnoid hemorrhage facial palsy hemiplegia cerebellar signs visual disturbances headache vertigo and convulsions

The vessels supplying the myocardium may be involved with the production of a large myocardial infarct or multiple small areas of necrosis Frequent attacks of precordial pain may be noted and the picture of congestive heart failure may ensue In hypersensitivity angiitis heart failure has been associated with miliary myocardial infarcts Heart failure may also be associated with the severe hypertension which is often present Pericardial tamponade may follow rupture of an aneurysm along a superficial coronary vessel

Pain in the chest may be due to pleural vasculitis and a hemorrhagic effusion may result Pulmonary vascular thrombosis leading to hemoptysis and excavation may simulate pulmonary tuberculosis An "anaphylactoid pneumonia has been described in cases which follow drug reac

are segmental in their distribution and involve arteries throughout most of the body in varying degree so that the resulting clinical picture is one of polymorphic manifestations which may seem unrelated Some observers have placed all of the pathological conditions of the vascular system characterized by inflammation and fibrinoid necrosis in the category of periarteritis nodosa including the angiitis which follows an allergic reaction to a drug or foreign protein Others have suggested necrotizing angiitis as a better term to use collectively for all vascular lesions showing this type of histological picture

Etiology and Incidence During the past few decades numerous observers have recorded vascular phenomena in association with allergic reactions of various types Gruber first suggested that periarteritis nodosa might be a general hyperergic reaction to infectious or toxic agents to which the vessel walls had previously been exposed In 1937 Clark and Kaplan described necrotizing vascular lesions accompanying serum sickness Rich and Gregory found lesions similar to those seen in periarteritis nodosa in patients dying from serum sickness and allergic reactions to sulfonamides and iodine These workers produced the lesions of periarteritis nodosa experimentally sometimes accompanied by glomerulonephritis in rabbits by the establishment of an anaphylactic state analogous to human serum sickness Hawn and Janeway using bovine serum produced segmental arterial lesions in the rabbit which were similar to those which followed the injection of horse serum Of interest was the production by the albumin fraction of lesions confined almost exclusively to arteries and by gamma globulin of lesions principally in the glomeruli and in a lesser degree in the heart However in most cases of periarteritis nodosa there is no history of any type of allergic reaction either to drugs or foreign proteins It has been suggested that various infectious agents may be etiological factors but little substantiating evidence exists

Zeek and her co workers believe that drug induced lesions are different morphologically and in distribution from those seen in human periarteritis nodosa and state that vascular changes like those described by Kussmaul and Maier have been produced experimentally by procedures that usually resulted in severe hypertension but did not cause hypersensitivity They prefer the term necrotizing angiitis for this entire group of arterial diseases and believe that five types may be differentiated (1) periarteritis nodosa (2) hypersensitivity angiitis (3) rheumatic arteritis (4) allergic granulomatous angiitis and (5) temporal or cranial arteritis Rose and Spencer believe that the presence or absence of lung lesions is a better basis for classification than the size of the involved vessels or the types of arteritis listed by Zeek The possibility of an infectious background is rekindled by the finding in their cases of pulmonary arteritis that a respiratory illness diagnosed as bronchitic pneumonic or asthmatic initiated the disease In two thirds of the cases over a year elapsed before systemic polyarteritis developed In many of their cases in which an association between a sulfonamide drug and polyarteritis was suspected the drug was given for a respiratory infection In five of twenty two cases a β hemolytic streptococcus was isolated and in addition 12 per cent had active rheumatic fever or a history of an attack

The nature of so called fibrinoid necrosis is fundamental to study of the pathogenesis of these various vascular lesions It is generally believed that this type of reaction in connective tissue is not pathognomonic of allergy but is merely a nonspecific response to injury Altshuler and Angevine have produced evidence that it represents the precipitation of acid mucopolysaccharides in the ground substance of connective tissue

The incidence is difficult to estimate when no specific diagnostic procedure other than the inadequate one of muscle biopsy is available Perhaps only a small percentage of the total instances of polyarteritis are recognized since selection on this present basis favors a high incidence of fatal cases Lesions tend to heal spontaneously and on biopsy are seen in all stages of histological development

It seems reasonable to conclude that there are a number of syndromes characterized by arterial inflammatory lesions and any sound classification will be impossible until more is known about etiology and pathogenesis There is ample evidence however that this group of diseases is being recognized more frequently

Males predominate with a sex ratio of 3 1 The peak age incidence is between twenty and fifty years

Pathology In periarteritis nodosa the arterial lesions consist of necrosis fibrinoid alteration and hyalinization of the media with a marked perivascular infiltration of mononuclear and polymorphonuclear cells but without foreign body giant cells The

Since prognosis is much worse in the presence of hypertension one would expect the majority of the untreated to die in the year following diagnosis (twelve of nineteen) Of the treated patients fourteen were living one year after diagnosis but no firm conclusion can be reached because of the unsatisfactory nature of the controls

In view of the rapid development of new therapeutic agents it is of importance that further information be obtained concerning the pathogenesis of periarteritis nodosa and so called hypersensitivity angiitis and whether there is any fundamental difference between them that cannot be explained by the nature and time-course of the antigen antibody reaction

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Cranial (Temporal) Arteritis

(Temporal Arteritis Giant Cell Arteritis)

This disease is essentially an arteritis and periarteritis of the temporal vessels characterized by a cordlike thickening of the involved arteries the presence of palpable nodules along the vessels and painful areas over the temples and scalp

Histologically there is proliferation of inflamed fibrous tissue of all layers of the affected vessels together with focal necrosis and granulomatous lesions associated with giant cell formation in the media The marked fibrous tissue proliferation in the intima leads to narrowing of the lumen and often to thrombosis The etiology is unknown but the onset in many cases follows an infection

There may be involvement of other arteries including the carotid subclavian coronary renal mesenteric pulmonary femoral brachial and dorsalis pedis

The onset is characterized by headache and other manifestations including malaise weakness anorexia loss of weight night sweats muscle and joint aches and soreness mild anemia and leukocytosis There may be pain in adjacent structures such as the scalp face jaws eyes and temporo mandibular joints The headache is boring in character usually more marked on one side severe at night and often intractable Two to four weeks after onset the temporal arteries become prominent and tortuous and along their course raised painful tender nodules may develop Pulsations later disappear The severity of the illness is out of proportion to the visible signs There may be enlargement of the cervical lymph nodes

In the majority of cases the disease is disturbing but self limited lasting from two to thirty months A variety of complications may ensue Ocular difficulty develops in about 30 per cent of the cases Pain photophobia diplopia oculomotor paresis or transient ptosis may occur and in more severe cases central retinal artery thrombosis or an ischemic optic neuritis with an edematous or pale papilla The clinical picture may be that of an acute retrobulbar neuritis Cerebral symptoms may develop with disorientation delirium hemiparesis or coma

This disease can simulate a cerebral tumor other types of cerebral vascular disease retinal artery thrombosis of varied etiology sinusitis dental neuralgia or osteoarthritis of the cervical spine

The chief value of the adrenocortical steroids in treatment is to control the progress of the arteritis as long as it is active and thus safeguard the degree of vision that remains or prevent the development of ocular complications Blindness does not correlate with the severity of the temporal artery involvement so that all cases should be treated as soon as the diagnosis is made All general symptoms disappear in a few days on steroid therapy including headache In one series the final incidence of blindness was 9 per cent in steroid treated cases while in a matched series untreated and analyzed retrospectively it was 22 per cent If there was loss of sight at the time treatment was begun no significant improvement followed steroid administration

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tions The association of asthma together with paresthesias of the extremities and eosinophilia was noted by Rackemann and Greene More recently Churg and Strauss have described a syndrome characterized by severe asthma fever and hypereosinophilia together with manifestations of vascular involvement in other organ systems which they have called allergic granulomatosis They feel that this is an entity apart from classic periarteritis nodosa and suggest that other allergic syndromes such as that of Loeffler may represent benign forms of allergic granulomatosis

Joint pains and myalgia have been frequently noted in periarteritis nodosa Muscle pain and soreness may be so prominent that when eosinophilia is also present trichinosis is suspected Joint swelling is rarely seen and often the tenderness or pain is associated with peripheral neuritis

In periarteritis nodosa the ovaries testes and epididymes are frequently involved Extensive vasculitis of the bladder may lead to gross hematuria and dysuria as an early manifestation of the disease

A variety of cutaneous lesions may be seen in periarteritis nodosa as well as in hypersensitivity angiitis These include scarlatiniform eruptions urticaria angioneurotic edema vesicular and bullous lesions The latter may become necrotic and ulcerate involving large areas of skin

Leukocytosis is often a prominent feature and in some cases a conspicuous eosinophilia is present A severe anemia may develop and marked elevation of the sedimentation rate is common

The *course* of periarteritis nodosa is variable The onset may be insidious or sudden due to a vascular thrombotic lesion The disease is usually fatal but cases have been reported which were characterized by remissions long intermissions and exacerbations Complete recovery may take place from hypersensitivity angiitis In both situations healing may occur clinically as well as histologically but when there is extensive involvement of the pulmonary cardiac renal or intraabdominal arteries recovery is rare

Diagnosis The diagnosis may be difficult as proof is dependent on histological evidence As the disease progresses many regions of the body may be involved and the multiplicity of signs and symptoms may suggest the correct diagnosis From the diversified symptomatology which has been described it is evident that periarteritis may simulate a great many other diseases When a biopsy is taken the skin and subcutaneous tissues as well as the muscle should be sent for microscopic section As the lesions in the vessels are segmental in distribution many sections must be made

It has been stated that the vascular lesions in polyarteritis are characterized by inflammation with marked cellular reaction in systemic lupus by necrosis with a peculiar fibrinoid change and in rheumatoid arthritis by an overgrowth of vascular elements Cases may be seen in which the manifestations of these syndromes both clinical and histological are present simultaneously In some of the clinical variants such as *Wegener's syndrome* in which there are necrotizing lesions in the respiratory tract generalized arteritis and focal glomerulitis and in "malignant rheumatoid arthritis all of these tissue changes may appear in well developed form The increasing frequency with which the lesions of periarteritis nodosa are being reported in patients with rheumatoid arthritis has been a cause for concern in view of the possibility that this may represent a deleterious effect of long term adrenal steroid administration

Treatment Treatment in the past has been for the most part symptomatic Every effort should be made to exclude any antigens that might be responsible Care should be taken in following the course of any patient receiving a drug to which manifestations of hypersensitivity may develop

Immediate relief of many of the manifestations of periarteritis are noted after the administration of adrenocorticotropic hormone and the adrenal hormones All histological signs of inflammation may disappear within a few weeks In the process of healing fibrous obliteration of the lumina of vessels may occur with resulting infarction particularly in the kidneys heart and intestinal tract Occasional cases have been reported in which complete spontaneous remission took place and the only difference in these cases and those treated with the hormones is the rapidity and extent of the healing

To determine the effect of adrenal steroid administration on length of survival Rose and Spencer compared the results in seventeen cases treated with cortisone since 1950 with nineteen control cases retrospectively analyzed in the precortisone period (1941 to 1950) The groups were similar with the important exception that hypertension was more common in the untreated group at the time of diagnostic biopsy (42 per cent) than in the treated group (6 per cent)

Since prognosis is much worse in the presence of hypertension one would expect the majority of the untreated to die in the year following diagnosis (twelve of nineteen) Of the treated patients fourteen were living one year after diagnosis but no firm conclusion can be reached because of the unsatisfactory nature of the controls

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In the majority of cases the disease is disturbing but self limited lasting from two to thirty months A variety of complications may ensue Ocular difficulty develops in about 30 per cent of the cases Pain photophobia diplopia oculomotor paresis or transient ptosis may occur and in more severe cases central retinal artery thrombosis or an ischemic optic neuritis with an edematous or pale papilla The clinical picture may be that of an acute retrobulbar neuritis Cerebral symptoms may develop with disorientation delirium hemiparesis or coma

This disease can simulate a cerebral tumor other types of cerebral vascular disease retinal artery thrombosis of varied etiology sinusitis dental neuralgia or osteoarthritis of the cervical spine

The chief value of the adrenocortical steroids in treatment is to control the progress of the arteritis as long as it is active and thus safeguard the degree of vision that remains or prevent the development of ocular complications Blindness does not correlate with the severity of the temporal artery involvement so that all cases should be treated as soon as the diagnosis is made All general symptoms disappear in a few days on steroid therapy including headache In one series the final incidence of blindness was 9 per cent in steroid treated cases while in a matched series untreated and analyzed retrospectively it was 22 per cent If there was loss of sight at the time treatment was begun no significant improvement followed steroid administration

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Progressive Systemic Sclerosis

(*Scleroderma Sclerema Adultorum Dermatosclerosis*)

Definition Progressive systemic sclerosis is a disease involving the collagenous connective tissue which may cause widespread symmetrical leathery induration of the skin followed by atrophy and pigmentation The cutaneous lesions are merely the external manifestation of a systemic disease and the muscles bones mucous membranes heart lungs intestinal tract and other internal organs may be involved by the same process resulting in functional impairment such as heart failure or pulmonary insufficiency

Etiology and Incidence The specific etiology of scleroderma is unknown Similar changes in collagen tissue may occur in systemic lupus erythematosus rheumatic fever rheumatoid arthritis and serum sickness but the pathological process is not of sufficient specificity to serve as a common denominator for the classification of these diseases The possible role of infections and of abnormalities of certain endocrine glands has been postulated but no consistent relationships have been noted

Both the localized form known as *morphea* and the generalized disease are relatively uncommon Scleroderma appears most frequently in the middle period of life and females are more frequently affected than males

Pathology Histological studies show that scleroderma is primarily a collagenous tissue alteration thus accounting for the stiffness and hardness of the affected structures There is at first swelling of collagenous intercellular substance which later becomes dense and sclerotic The vascular lesions show thickening of the intima often with fibrinoid degeneration and occlusion resembling those seen in systemic lupus erythematosus and are thought by some to have a relationship to the scleroderматous alterations in the skin Later there is atrophy of the epidermis including the appended structures Calcification develops in some cases Similar changes occur in collagen tissue in other organs including the heart lungs and gastrointestinal tract

Characteristic renal lesions have been reported in which there is thickening of the intima principally of the interlobular arteries as a result of the deposition of a mucoid substance which is metachromatic With progression of the lesion the vessel lumen is narrowed or occluded by the formation of concentrically laminated fibrous tissue leading to patchy areas of cortical necrosis This sequence of the deposition of metachromatic ground substance preceding the fibrogenesis of collagen is characteristic of both embryogenesis of connective tissue and its formation in wound healing Experimentally certain naturally occurring mucopolysaccharides induce active fibrogenesis It has been postulated that the formation of an abnormal mucopolysaccharide in the body might be the basis for the development of this disease However these changes in the kidney as well as the fibrinoid lesions in the arteriolar and glomerular thrombi are similar to those seen in accelerated nephrosclerosis

Symptoms and Signs The focal form of the disease is characterized by indurated lesions found on the trunk extremities or neck which may follow the distribution of the peripheral nerves This is a benign process which only rarely may precede the development of diffuse cutaneous or visceral involvement In the linear form firm irregular bands several centimeters in width may be distributed over the skin of the extremities forehead and scalp but seldom the trunk There may be involvement of underlying muscle and the development of contractures

In the diffuse or systemic disease the cutaneous changes pass through several stages the first of which is a brawny edema which commonly starts on the hands and feet and later involves the face neck and often the trunk The nonpitting edema gives the skin a puffy white appearance with smoothing of the normal folds In the second or indurative stage the skin becomes smooth waxy leathery and tight so that it cannot be lifted from the deeper structures This may be most prominent on

the fingers dorsum of the hands and the ankles The face becomes masklike with the expression fixed Constitutional manifestations such as weakness and loss of weight are common and joint pains and fever are prodromal symptoms in many cases Raynaud s phenomenon and sclerodactyly often associated with dysphagia due to esophageal involvement may be present for years before cutaneous thickening in other areas is noticed This has been referred to as the acrosclerotic form The Raynaud s phenomenon may be of the anemic type which is a chronic condition different from the true spastic phenomenon characterized by sudden attacks

As the disease advances to the atrophic stage the skin becomes thinner smoother and completely adherent to the shrunken muscles The movement of joints is progressively restricted until the patient resembles a living mummy There may be extensive brownish pigmentation of the skin as well as patchy areas of depigmentation In some cases calcium is deposited in the diseased portions usually about joints Other developments include anhidrosis coldness of the digits loss of hair telangiectasia and the appearance of indolent painful ulcers Lesions may also be noted in the mucous membranes with painful induration of the tongue as well as of the gums In some cases dyspnea cyanosis and edema are attributable to involvement of the heart muscle by this peculiar type of fibrosis Diffuse pulmonary scleroderma may result in severe functional impairment with the syndrome of "diffusion fibrosis due to impairment of oxygen transport across the alveolo-capillary membrane similar to that seen in sarcoidosis and beryllium intoxication Ventilatory function may also be impaired if involvement of the skin and muscles restricts normal motion of the chest Disturbances in thyroid pancreatic pituitary and adrenal function have been described by various observers although these organs may show no histological lesions characteristic of this disease The difficulty in swallowing is the result of atrophy and sclerosis of the esophagus leading first to dilatation and loss of normal peristaltic movements Later there may be partial obstruction with the development of a chronic esophagitis When there is diffuse involvement of the intestinal tract pain nausea vomiting diarrhea or constipation may develop Deterioration of renal function complicated by a malignant type of hypertension may develop as a late manifestation Severe hypertension of sudden onset may occasionally appear before there are signs of renal insufficiency The association of cataracts premature graying and baldness calcification in subcutaneous tissues osteoporosis hypogonadism and scleroderma is heredo familial and is known as *Werner s* or *Rothmund s syndrome*

In contrast to other connective tissue diseases such as systemic lupus erythematosus hematological and biochemical alterations are not regularly present There may be a mild anemia and increase in the sedimentation rate Serum albumin may be below normal levels and occasionally some elevation in serum globulin is noted The urine may contain albumin red cells white cells and casts Roentgenograms may reveal diffuse osteoporosis and destructive lesions of bone have been described Involvement of the heart lungs and intestinal tract may be recorded also by radiological and electrocardiographic studies The roentgenographic appearance of the lungs is usually a diffuse linear infiltration which may be more prominent in the lower half of the lungs There may be dilatation of the esophagus with marked delay in the descent of barium A triangular appearance of the heart and limited movements on fluoroscopy may suggest the changes noted in pericardial effusion and myxedema heart The electrocardiogram may show change in rhythm T wave alteration and other evidence indicative of myocardial involvement These changes are not specific or diagnostic of scleroderma

Diagnosis The typical case presents no difficulties in diagnosis but sclerodactyly in the early phases may be diagnosed as Raynaud s disease or the joint pains as some type of arthritis Fever arthralgia and erythema of the skin may suggest systemic lupus erythematosus and the distinction from dermatomyositis is at times difficult In the stage characterized by edema differentiation must be made from scleredema which is a relatively benign condition Probably the majority of cases of scleredema are diagnosed as scleroderma and this may account for many of the instances in which dramatic improvement in scleroderma is believed to have occurred The hands which are so uniformly involved in scleroderma are almost always spared in scleredema Scleredema does not progress to atrophy contractures or pigmentary changes and spontaneous remission is the rule There may be pleural or pericardial effusion in scleredema but seri

ous involvement of the heart lungs esophagus or intestinal tract is not characteristic as in scleroderma

Other conditions which may be characterized by some type of cutaneous edema are in most instances easily differentiated These include trichinosis myxedema and edema of cardiac or renal origin

Prognosis In the localized type (morphea) healing takes place leaving a smooth hard depressed area in the skin Scleroderma of the slowly advancing generalized type may pass through periods of activity and remission during which extension to a new area may be accompanied by remission in areas involved earlier Disability may finally be extreme and death in the chronic form often results from some intercurrent infection or from specific involvement of such areas as the heart lungs or kidneys

Treatment The long list of therapeutic agents tried in this condition including various metals hormone preparations and peripheral vasodilators makes it obvious that no specific treatment has been discovered Local heat massage hydrotherapy and softening ointments may be beneficial In the vascular form with vasospasm and a formal vasodilatory response protection from cold vasodilator drugs and sympathetic ganglionectomy may be recommended according to the principles and with the limitations followed in the treatment of Raynaud s disease A number of cases have now been treated with pituitary corticotropin or cortisone With aggressive therapy temporary beneficial effects may be obtained in the early phases but treatment after the development of atrophy and contractures has not been helpful No improvement in pulmonary function has been observed to follow hormonal therapy

Most important is the intelligent utilization of physiotherapy to prevent deformities resulting from contracture and to maintain muscle function to the greatest possible extent

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Scleredema

(*Scleredema Adultorum of Buschke*)

This rare condition which usually follows an acute infection and has a benign course is characterized by a brawny edema of the skin which may resemble closely the early stage of scleroderma The dermis is thickened and there is a moderate perivascular cuffing with mononuclear cells In the deeper layers the collagen fibers are hypertrophied and swollen A mucin like material which stains with cresyl violet may separate these enlarged collagen bundles producing a fenestrated appearance Similar changes have been described in other organs

Scleredema has been considered to be a diffuse disease of collagen It usually develops one to six weeks after an infection which is most frequently of streptococcal origin The disease is predominantly one of females The majority of cases develop in childhood and early adult life but the diagnosis has been made in the neonatal period and as late as the seventh decade

The characteristic waxy brawny edema of the skin usually appears abruptly although a brief prodromal period with slight fever malaise and myalgia has been described In the majority of cases the neck is involved first but within one to two weeks there is spread to the face chest abdomen and extremities The hands and feet are almost always spared There may be an erythematous blush to the involved skin but pigmentation and atrophy do not develop There is no pitting on pressure and the skin is difficult to pick up There is a sense of being "hidebound and when the chest is involved dyspnea may result from the restriction of thoracic movement Involvement of the tongue and pharyngeal tissues results in dysphagia and dysarthria Parotid swelling has been described and the occasional development of hydrarthrosis pleural effusion and hydropericardium is cited as evidence of the systemic nature of this disease

Scleredema and the early stage of scleroderma may be easily confused The onset of scleroderma may also follow an infection and the histological changes seen at this stage may not be distinctive In scleredema the induration is more prominent in the superficial layers of the cutis and atrophy pigmentation and telangiectasia do not develop In contrast to scleroderma

involvement of the hands and feet is rare The early phases of dermatomyositis may resemble scleredema so closely that a final diagnosis must be delayed until the more distinctive features appear Other conditions such as trichinosis myxedema and edema of cardiac and renal origin are easily distinguished by the associated manifestations

There is resolution of the edema in from six to eighteen months in most of the cases However the disease may remain essentially static for years or may regress in certain areas leaving islands of edema which slowly resolve

As in scleroderma many forms of treatment including artificial heat hormonal substances vasodilators and antihistamines have been tried but thus far none may be considered specific The general tendency to spontaneous recovery makes evaluation of therapy difficult In cases treated intensively with pituitary corticotropin or adrenocortical steroids there may be partial clearing of the edema but the response is usually not dramatic

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Thrombotic Thrombopenic Purpura

This syndrome is characterized by thrombocytopenic purpura hemolytic anemia and bizarre symptoms and signs of central nervous system involvement The histological picture consists of occlusions of small arterial vessels by an amorphous acidophilic material It was first thought that these were platelet thrombi but endothelial damage appears to be the first event and it has been demonstrated that the material is composed of an immunochemically reactive derivative of fibrinogen or fibrin The thrombotic lesions are commonly seen in the myocardium adrenals renal cortex pancreas and gray matter of the brain They show various stages of healing and recanalization may be seen In some cases there is the simultaneous presence of the vascular lesions of systemic lupus erythematosus and polyarteritis

The disease usually presents as an acute process with a fatal outcome in days or weeks but occasionally it is a chronic relapsing disease lasting for months to years appearing in episodic bouts and ending in death from an acute exacerbation The clinical and laboratory manifestations of the thrombocytopenic purpura are similar to those seen in purpura due to other causes

The onset is usually associated with malaise headache fatigability myalgia or arthralgia Fever is regularly present and nausea vomiting and abdominal pain are frequent Pallor is conspicuous icterus when present is usually mild Hepatosplenomegaly and lymphadenopathy may be observed Cardiovascular manifestations include tachycardia gallop rhythm and a systolic bruit Psychotic behavior may be the presenting feature and among the nervous system manifestations are irritability confusion delirium and stupor Convulsions occur as well as focal signs including cranial nerve palsies hemiplegia and aphasia The manifestations may wax and wane in severity and are often transitory

The anemia is normochromic and normocytic and the hallmarks of a hemolytic process are present The abnormally shaped erythrocytes noted are designated as helmet cells " "schizocytes " or "bizarre spherocytes " In the occasional case there is a positive Coombs test The white cell count may be elevated with a leukemoid reaction L E cells have been demonstrated in a few instances At times the diagnosis is made by noting the typical vascular pattern in paraffin sections of particles obtained on bone marrow puncture

Transfusions do not elevate the erythrocyte level for a prolonged period unless a spontaneous remission occurs Adrenocorticotropic hormone or adrenocortical steroids have not had a dramatic effect but may be tried in large doses In two cases there has been relief of the hemolytic process after splenectomy

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Diseases Due to Physical Agents

Heat Exhaustion, Heat Stroke and Heat Cramps

Heat exhaustion is a physiological breakdown following exposure to heat and is characterized principally by peripheral vasomotor collapse *Heat stroke* on the other hand has for its distinguishing manifestation an extreme elevation of body temperature *Heat cramps* are muscular cramps due to excessive salt loss Although manifestations of two or even all three of these conditions may coexist the mechanisms by which they are produced are quite different

Heat exhaustion results usually from physical exertion in a hot environment when vasomotor control and cardiac output are inadequate to meet the needs of increased skin circulation in addition to muscle and cerebral circulation It may be precipitated in even the most fit man by heavy enough work or a severe enough environment The severity of the environmental heat stress is determined by temperature humidity and wind velocity The wet bulb temperature is probably the best single index paralleling physiological stress

Heat exhaustion is a nonfatal physiological disturbance unless complicated by coexisting disease The factors in normal adaptation are important in understanding the morbid physiology When a man is exposed to a hot environment a considerable part of his circulation must be directed into the blood vessels of the skin in order to radiate heat from the surface and to support activity of the sweat glands The ease of these adaptations is rapidly enhanced by repeated exposures to work in the heat a process known as acclimatization caused at least in part by increased adrenocortical activity and manifested by increased blood volume better vasomotor control and more efficient sweating Obviously even a minor degree of dehydration will prevent maximum cardiovascular adaptation and so predispose to heat exhaustion

Salt deficiency from any of several causes predisposes to heat exhaustion Restricted salt intake or lack of supplemental salt during very heavy sweating is a common cause of salt deficiency Recently described excessive salt concentrations in the sweat of patients with fibrocystic disease of the pancreas and in some normal members of their families illustrate another rather special mechanism of salt depletion

Faintness usually with subjective sense of palpitation is the predominant symptom Nausea vomiting syncope headache and restlessness are common Other symptoms may appear from underlying cardiac or other disease

The patient who has collapsed in the heat and is perspiring freely almost surely has heat exhaustion and not heat stroke even though his temperature is somewhat elevated Under general supportive treatment he will usually recover consciousness promptly unless dehydration salt deficiency cardiovascular disease or some other complicating condition is important in the picture In older patients a cardiovascular complication should be suspected if the symptoms persist

The *prognosis* of simple heat exhaustion is invariably good and the *treatment* is simple Rest in a comfortable environment

and mildly salted fluids by mouth as tolerated will usually suffice Occasionally when vomiting is severe and cardiac disease is absent intravenous injection of 1000 ml of 5 per cent glucose in physiological saline may hasten recovery The most important phase of treatment is that related to cardiac or vascular disease which may manifest itself

Heat stroke is a failure of adequate heat elimination almost always related to a breakdown of the sweating mechanism it may occur whenever heat regulation is dependent on sweating for long periods of time Experimentally the rate of sweating in normal persons has been found to decrease progressively during work in the heat and finally to lead toward real deficiency of sweating In heat stroke this process has apparently gone on to complete breakdown of the mechanisms of temperature regulation to complete cessation of sweating and extreme elevation of body temperature

At autopsy the important and primary tissue damage is in the central nervous system consisting in edema and in severely involved areas destruction of nerve cells chiefly in the cerebral cortex Other changes are probably related to the secondary vasomotor shock which occurs in severe cases congestion edema and hemorrhages in various organs

Although the exact mechanisms of maintenance of sweating are not known it is clear that they fail in incipient heat stroke and the process behaves like a local fatigue of the glands Heat stroke rarely occurs if relief from sweating is afforded during a part of the day such as in desert areas with cool nights or where air-conditioned sleeping quarters are available In extremely hot environments the development of full blown stroke may be a matter of a few minutes after cessation of sweating since all the normal heat loss under these conditions may be by evaporation of sweat Dehydration is not a factor in fact super hydration has been reported Leukocytosis is the rule often above 20 000 per cubic millimeter diminution of platelets is common in severe cases

The patient may occasionally be aware of cessation of sweating but often he is not Sensation of extreme heat is the rule The first overt symptoms are often those referable to the central nervous system mental confusion staggering gait headache delirium or coma In the early phases the circulation is maintained (rapid full pulse) but soon a stage of vasomotor collapse supervenes with low blood pressure and rapid weak pulse

The *diagnosis* of heat stroke is no problem in the classic instance with warm dry skin temperature of 105 F or higher history of long exposure to heat lack of evidence of other cause and coma or near coma The chief confusion is with other diseases of the central nervous system causing coma and hyperpyrexia and occasionally with overwhelming sepsis without external manifestations or terminal liver disease In some instances therapy to lower the temperature should be given before a sure diagnosis is made

True heat stroke calls for heroic measures and is one of the few true medical emergencies The aim of *treatment* is to reduce the body temperature to a safe range (102 F or lower) as rapidly as possible since brain damage is a function of both temperature and time Total immersion in an ice bath or in water as cold as possible is probably the most efficient method of cooling The alleged danger of heat retention from peripheral vasoconstriction and of increased shock has not been supported experimentally or clinically Evaporative cooling by sprays and fans is effective provided the environment is cool and dry enough to allow rapid evaporation An important adjunct often neglected is vigorous massage of the extremities during the cooling to overcome the peripheral stagnation regularly seen and to allow the more rapid transfer of heat Vigorous cooling should be stopped when the rectal temperature reaches 102 F but may need to be reinstituted if the temperature rises again Intravenous fluids should be given with care and only with definite indications because of the dangers of pulmonary edema Persistence of coma and shock after cooling probably means severe brain damage and therapy is often disappointing Irregularity of temperature regulation is to be expected for several days in those who recover

Prognosis is wholly a function of the promptness of treatment All untreated patients will die Probably all would recover if heat stroke were detected early and treated vigorously Most of those who have recovered retain some intolerance to heat Late effects of brain damage are possible but have not been reported frequently

Heat cramps are painful contractions of various skeletal muscles a symptom most commonly seen among manual workers in hot environments whose body fluids have been depleted of sodium chloride by unre

placed heavy losses (up to 20 gm a day) in sweat The diagnosis is made by a marked lowering of plasma chloride (often to 90 mEq per liter) in the presence of the clinical symptoms It is evident that factors other than simple salt depletion are acting in this condition since the symptom of cramps is only occasionally seen in patients with cardiac or hepatic disease with a similar degree of salt depletion from low salt diet and diuretics The cramps are specifically relieved by the replacement of salt (and water) The intravenous administration of 600 to 1000 cc of normal saline may be necessary to start relief of acute symptoms More important is prevention which is most surely achieved by adding 0 1 per cent sodium chloride to drinking water Heavy salting of food and the use of salt tablets are effective but more difficult to enforce

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Decompression Illness

(*Caisson Disease*)

This term refers to the group of symptoms produced by the sudden reduction in pressure of the atmosphere It is seen (1) among workers in compressed air after return to atmospheric pressure (caisson workers tunnel workers and deep sea divers) or (2) on rapid ascent in open airplanes to heights usually above 25 000 feet The recent popularity of deep diving as a sport has exposed a larger number of persons many of them unwarned and untrained to the possibility of decompression illness It should be noted that in all instances the symptoms occur during or after an abrupt drop in atmospheric pressure always to at least one half of the initial pressure and usually to one third or less Since the pressure in water increases one atmosphere for each 33 feet in depth dives of more than 60 to 70 feet if prolonged introduce some hazard in this respect

Etiology All the manifestations except an occasional symptom are clearly due to the evolution of bubbles of nitrogen in the tissues and blood stream The nitrogen in solution at the higher pressure is freed by the lowering of pressure Nitrogen is the gas chiefly concerned because the pressure change of this gas is greatest and because oxygen and carbon dioxide diffuse rapidly and chemically combine more readily although the latter gases do diffuse into nitrogen bubbles when once formed Bubbles cause symptoms by plugging small vessels and by the pressure of their expansion particularly in confined regions

Morbid Anatomy Actual bubbles have been demonstrated only rarely The usual cause of death is damage to the central nervous system most severe in the spinal cord especially the lower thoracic region In the early stages there are areas of nonspecific softening later replaced by gliosis Frequently the pathological changes are more widespread than suspected from clinical findings

Bone changes are those of small sterile infarcts In sudden deaths there is frequently intense congestion of all the internal organs

Pathological Physiology The amount of nitrogen dissolved in the tissues of the body at any pressure is considerably more than would be dissolved in a similar volume of water This results from the greater solubility (five times as great) of the gas in fat than in water The high lipoid content of the central nervous system is the chief factor causing the vulnerability of that tissue

Gradual reduction in the pressure of nitrogen will result in harmless diffusion of dissolved nitrogen from the tissues into the blood stream and elimination by the lungs It is only by marked reduction in pressure (to one half or greater) that bubbles may form Even then a solution (or the tissues) may remain supersaturated unless disturbed Thus trauma and exercise predispose to bubble formation (and symptoms) and often determine the site The circulation of the tissues is another important factor relatively ischemic tissues will retain nitrogen longer

Nitrogen may be removed prophylactically from the tissues by reducing the nitrogen content of the gas breathed without danger of bubble formation Thus

breathing 100 per cent oxygen for 3 hours before high altitude ascent will practically eliminate the incidence of symptoms At pressures above two atmospheres however oxygen is highly toxic and therefore its use in compressed air work must be limited to an aid in the later stages of gradual de compression Helium chiefly because of its rapid diffusion has become an important replacement for nitrogen in work at very high pressures such as in deep-sea diving

Symptoms The onset of symptoms occurs usually from a few minutes after decom pression to three hours later By far the most common manifestation is pain in joints muscles or periarticular tissue (the "bends") coming on usually suddenly in one or several joint regions and varying in intensity from a mild ache to a tearing excruciating pain Mild pains may disappear with rubbing Very severe pain may lead rapidly to collapse

Manifestations in the skin considered among the mild forms of the disease con sist in itching either mild or severe usu ally with blotchy purplish erythema some times with a mild degree of edema and oc casionally with palpable crepitation

Neurological symptoms are of grave im portance The lower extremities are the chief site They may vary from mild pares thesia and weakness to total paralysis Loss of control of bladder and rectal sphincters is almost invariable even with little other paralysis Symptoms from higher cord le sions are much less common and rare from brain damage

Symptoms from bubbles in the lung capil laries (the "chokes") are often indicative of a severe form of the disease The patient complains of inability to take a satisfactory deep breath constriction of the chest and a dry cough Severe symptoms may progress rapidly to general collapse resembling asphyxia

In severe forms of the disease resulting from accidents and sudden escape from high pressures rapid collapse and sudden death may occur without premonitory symp toms

This description is more strictly that of decompression after work in compressed air In decompression to high altitude in volvement of the nervous system is much less frequent otherwise the symptoms are quite similar

Diagnosis Correct diagnosis depends en tirely on a history of recent exposure to compressed air The high altitude syndrome will be met only *during* high altitude flight Without adequate history the condition cannot be surely distinguished from other conditions causing muscle and joint pain or spinal cord disease Occasionally abdom inal pain due to decompression might be confused with acute peritonitis

It is well to distinguish carefully the symptoms of decompression illness from other symptoms due to pressure change Painful ears and sinuses occur chiefly on *increase* in pressure Nitrogen at high pres sures has a narcotic effect seen again on *increase* not decrease in pressure Intes tinal gases may cause pain by simple ex pansion *during decompression*

Treatment and Prognosis The sole effec tive treatment is recompression and gradual decompression At high altitudes descent to 20 000 feet will usually suffice The syn drome after compressed air requires a com pressed air chamber in which the patient should be recompressed to his original working pressure Except in some instances of cord damage symptoms will usually disappear provided treatment is prompt enough

Decompression after relief or control of symptoms should be gradual usually last ing 2 to 3 hours and recompression again is indicated by any recurrence of symp toms Details of management may vary markedly Breathing oxygen during the later stages of decompression helps to remove nitrogen

Prognosis is invariably good if there is no cord damage Even then prompt recom pression is often successful Recovery of cord function after more than transient damage is variable some patients with complete physiological cord transection make a gradual complete recovery others are permanent paraplegics Other residual defects are related to the bones which may *show permanent radiographic change of* "aseptic infarction" at the ends of long bones and be the site of secondary hyper trophic changes

Medical management of the workers by elimination of elderly obese and particu larly susceptible men and by well con trolled slow decompression after work periods has reduced and can continue to reduce both the incidence and severity

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High Altitude Sickness

Man is exposed to high altitude in two quite different situations in airplane flight and in residence or climbing in high mountainous areas The illnesses associated with these two modes of stress are conventionally discussed separately However there is logic in a combined presentation provided the discussion is limited to the effects of low barometric pressure The physiological stimulus is essentially the same although the speed of onset of the stimulus and its duration are usually quite different The reader may need to consult specialized texts in aviation and mountain medicine regarding the various associated stimuli such as acceleration motion cold etc

The relation between altitude and barometric pressure is readily seen in Figure 47 It will be noted that barometric pressure is approximately halved at 18 000 feet and cut to one third at 28 000 feet Since the air is of constant composition within the range of airplane travel the partial pressure of oxygen exactly parallels the barometric pressure However this parallelism does not extend to alveolar oxygen pressures because of the introduction of water vapor and carbon dioxide in the alveolar spaces Regardless of the altitude the water vapor pressure in the alveoli is 47 mm of mercury The alveolar carbon dioxide pressure although lowered by hyperventilation at altitude amounts to 25 to 30 mm of mercury The combined pressure of carbon dioxide and water of over 70 mm of mercury causes the alveolar O pressure to decrease more rapidly than the barometric pressure In theory at least the alveolar O pressure is zero at a barometric pressure of approximately 70 mm of mercury even when pure oxygen is breathed

The relationship between alveolar pressure and altitude while breathing air or oxygen is shown in Figure 48 The same figure also shows the arterial oxygen saturation under the same conditions Because of the shape of the curve of affinity of hemoglobin for oxygen the arterial oxygen saturation falls off very gradually as the alveolar PO is reduced and then more rapidly Altitudes below 5 000 feet cause almost no arterial hypoxia between 5 000 and 10 000 feet the hypoxia is slight at higher altitudes successive increments in altitude have increasingly greater effects

Acute altitude sickness or acute mountain sickness is the syndrome occurring immediately or after a few hours exposure to altitude high enough to cause significant hypoxia In any one individual the symptoms will depend on the circumstances of the exposure and the altitude attained In airplanes the first symptom is usually an impairment of mental function rather similar to that induced by alcohol or marked lowering of blood sugar Fine judgment is earliest affected disorders of speech and of delicate coordination appear at somewhat higher altitudes The person so exposed may be unaware of any disorder or may experience some lightheadedness

In mountain exposure the first symptom is likely to be breathlessness especially during exertion it may appear at lower altitudes than in airplanes because physical exertion is more commonly required on mountains than in airplanes Arterial hypoxia of 85 to 88 per cent saturation regularly stimulates pulmonary ventilation through the carotid and aortic bodies but the hyperventilation so induced may be subjectively felt only during exertion Doubling of pulmonary ventilation at rest may not cause any awareness to the subject Along with the early breathlessness at moderate altitude the person may have mild cerebral symptoms (lightheadedness etc) due in part to the alkalosis of hyperventilation

If the exposure is continued for several hours headache malaise and in severe cases prostration may supervene People vary markedly in their susceptibility to these symptoms The reasons for differences in susceptibility among young normal persons are poorly understood As might be expected older people and patients with cardiovascular disease cerebral vascular disease and chronic diffuse pulmonary disease show greater susceptibility to symptoms which may be serious or even fatal Medical advice in regard to airplane or mountain travel for older people or patients with pulmonary or vascular disease cannot be generalized specific knowledge of the expected altitude exposure and of the patient s clinical status is necessary Modern commercial aircraft are almost all pressurized so that cabin pressure is kept at

the equivalent of 5 000 to 8 000 feet altitude *Stress of modern airplane travel is* likely to be greater from anxiety than from altitude Mountain travel or residence is apt to be a greater stress for the above group of patients than airplane travel partly because of the greater exertion likely to be involved

The syndrome of acute altitude sickness at moderate altitudes usually subsides in a few hours or days For an understanding of this phenomenon as well as of reactions at higher altitudes it is necessary to consider *the process of altitude acclimatization*

The first and most striking change in *acclimatization* relates to pulmonary ventilation Acclimatized persons breathe more deeply and slightly more rapidly than the unacclimatized with the result that their alveolar oxygen pressure is higher In other words the gradient in oxygen pressure from the atmosphere to the alveoli is reduced At least in part these advantageous changes are caused by the renal compensations of

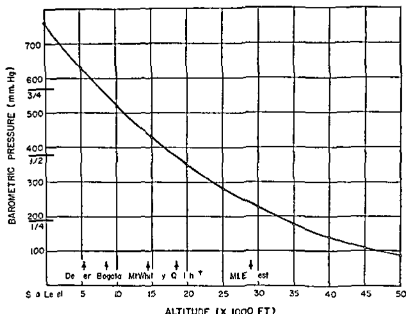


Fig 47 Relationship between atmospheric pressure and altitude
† Aucanquilcha Chile highest permanent habitation

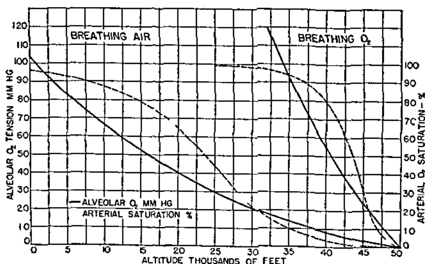


Fig 48 The alveolar oxygen tension and the percentage oxygen saturation of the arterial blood at various altitudes while breathing atmospheric air and while breathing oxygen (Armstrong H G Principles and Practice of Aviation Medicine 3rd ed Baltimore Williams and Wilkins Company 1952)

chloride retention which allows a reduction of plasma bicarbonate with minimal elevation of pH during hyperpnea Prior to this phase of acclimatization the respiratory drive from hypoxia through the carotid receptors is reduced by the respiratory depression from alkalosis through the respiratory center

Another pulmonary change of probable importance is an increase in the pulmonary vascular diffusing surface as measured by figures for diffusing capacity The mechanism of this adaptation is not wholly clear

Early studies of altitude acclimatization emphasized polycythemia as the mode of adaptation This change is real but of limited physiological significance The highest values recorded are in the order of a 50 per cent increase in oxygen-carrying capacity of residents on the highest Andean plateaus Values for residents at lower altitudes and for temporary residents in the Andes are much lower It is evident that full acclimatization in this regard takes many months If we consider as Riley emphasizes that acclimatization is the sum total of adaptations whereby the gradient of oxygen between the atmosphere and the tissues is reduced it can be calculated that polycythemia may reduce the gradient by 2 or 3 mm of mercury whereas hyperventilation may reduce it 10 to 15 mm of mercury It is doubtful that the full theoretical advantage of polycythemia is gained because of the increased viscosity of polycythemic blood

Other changes in acclimatization are less fully explained Changes in the affinity of blood for oxygen are in some dispute among observers and are relatively small in any case Observations of increased myoglobin in muscle are probably significant The increased bilirubin in blood is similar to that found in other polycythemias

It is logical that there is also acclimatization at a local cellular level probably in many tissues but most clearly demonstrated in germinal cells Decreased fertility of humans and domestic animals brought to altitudes above 15 000 feet is a common observation Restoration of fertility observed histologically as well as in population studies is probably one of the last manifestations of acclimatization

The subject of *chronic altitude sickness* is of theoretical interest although it has been observed and recorded only in the high Andean plateaus above 15 000 feet As described by Monge it has all the chief clinical features of polycythemia vera including plethora vascular occlusions in various vital organs ulcerations and bleeding in the gastrointestinal tract sometimes cardiac failure and if untreated results in death Its main difference from polycythemia vera is that it is completely relieved by transporting the patient to sea level Although some of the reported cases may have had complicating cardiovascular disease of other cause it is likely that the disease is an example of the vascular difficulties imposed by the viscous blood of polycythemia It is of interest that in the vicuna and other animals living at high altitude species adaptation is not by polycythemia but by increased concentration of hemoglobin in cells and by increased affinity of their hemoglobin for oxygen

Acclimatization for *high altitude aviation* probably does not occur In other words repeated short exposures to hypoxia are not effective stimuli to adaptation Even eight hour daily exposures cause very minor improvement in tolerance

As mentioned briefly earlier the effect of altitude in aircraft is peculiarly insidious particularly on mental processes With no real acclimatization possible the effects of an altitude of 15 000 to 18 000 feet for example are more severe than in the mountains Dangerous collapse is not uncommon and is well documented in aircraft misadventures as well as in experiments with low pressure chambers

Pressurization of aircraft cabins essentially avoids high altitude exposure from aircraft travel provided ventilation is sufficient to prevent CO accumulation Oxygen inhalation by the demand type of mask as used in some military aircraft prevents hypoxia up to altitudes of about 40 000 feet but in this range the effect of lowered barometric (and nitrogen) pressure is a major factor At about 25 000 feet dissolved nitrogen in the blood and tissues comes out of solution causing a syndrome similar to that of decompression illness from high pressure work (See section on Decompression Illness) For special aviation work pressure suits have been devised to raise the ceiling of flight in nonpressurized aircraft

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Blast Injury

Blast injury is the term applied to the physiological disturbances and internal structural damage caused by the pressure wave from an explosion The blast injury itself is not characterized by evidence of injury on the body surface but it frequently occurs concomitantly with other forms of trauma In this discussion we are not concerned with the purely psychiatric syndrome which also has been labeled blast injury

The rapidly expanding gases from an explosion generate a sharp rise in pressure in the surrounding zone of air or water this pressure wave is then propagated in a manner analogous to the transmission of a single sound wave When this pressure wave meets a human body it has little effect on solid organs and tissues but may cause rapid and damaging distortion of those tissues containing air such as the eardrums the lungs and the intestinal walls The amount of damage is related fairly closely to the maximum pressure of the wave pressures between 3 and 15 atmospheres cause detectable but not necessarily fatal injuries to the lungs in animals

Minimum trauma in the lungs consists of petechial hemorrhages mostly on the lung surfaces between ribs If the hemorrhages are at all extensive secondary edema occurs in the hour or two after injury and local areas of emphysema are common In more intense blasts the hemorrhages occur more widely in the lung and involve larger vessels so that gross blood may escape into bronchi and trachea In the intestines trauma consists similarly in mild cases of intramural hemorrhages in severe cases of rupture The colon and lower small intestine are most often involved Lung injuries are predominant in air explosions in water the incidence of intestinal injuries is considerably increased Hemorrhages in the brain are caused occasionally apparently the pressure is transmitted from the great vessels in the thorax to the cerebral vessels

The person suffering blast injury in air will usually be bowled over by the explosion and most likely rendered temporarily unconscious When conscious he may be dazed almost surely he will have ear pain and partial or complete deafness but otherwise he may have no symptoms If the lungs are injured he will soon complain of dyspnea and chest pain which may progress rapidly If the damage is severe cyanosis will become apparent and blood may appear in the sputum Severe blood loss into the lungs not infrequently leads to shock Abdominal symptoms are rare in air blast injury and when present are found usually in association with severe lung injury In immersion blast injury the abdominal symptoms often predominate and vary from the mild pain of a few petechial hemorrhages to the acute abdominal catastrophe of intestinal rupture

The primary point of diagnosis lies in the recognition that internal injuries may exist without external evidence of trauma Even if burn fractures or lacerations are present the possibility of blast injury should be kept in mind The presence of damage to eardrums adds greatly to the suspicion of internal blast injury Bradycardia often extreme has been frequently noted and may be a useful diagnostic sign

Prognosis in air blast injury depends almost entirely on the extent of pulmonary damage Grossly bloody sputum is a dire prognostic sign as is intense cyanosis or shock

Treatment is primarily aimed at the relief of dyspnea and anoxia by the use of inhalation oxygen tracheal aspiration and rest Since shock if present is associated with internal blood loss whole blood transfusion is the treatment of choice Treatment of the rarer manifestations in other organs is that of internal trauma to these organs from other cause

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Motion Sickness

(*Air Sickness Sea Sickness*)

Air sickness and sea sickness may be defined as conditions due to frequently repeated oscillatory movements of the body in a ship or airplane and characterized by dizziness nausea vomiting pallor and sweating

Etiology In a ship the pitching see saw movement on a transverse axis through the center of the ship the rolling movement on its long axis and the movement of the entire ship up and down constitute the usual motions to which a person is subjected In airplane travel vertical accelerations and excessive rotary motions bring on the disturbance Recent evidence indicates that the basic cause of air sickness is violent head motion which affects the fluid in the labyrinthine channels of the inner ear Visual psychogenic and kinesthetic factors play a subsidiary role varying with the person

Symptoms The symptoms may come on without warning A man who was previously in good spirits may suddenly become quiet and subdued He feels nauseated and is aware of excessive salivation Mental depression is almost constantly present Vomiting may then take place with mild headache Pallor and cold sweats are common true vertigo is rare There are no characteristic objective signs although a drop in systolic blood pressure has been reported accompanied by tachycardia or a slow pulse rate The nervous component in both air and sea sickness is at times important

Treatment Fixing the eye on a definite object in space undoubtedly is of real help in both air sickness and sea sickness The eye should not be allowed to shift with the position of the airplane for the earth or sky will swim past the eyes and produce dizziness or nausea in a manner comparable to the development of this condition when one whirls rapidly on a piano stool Head rests in airplanes have significantly decreased motion sickness When possible travelers should place their heads firmly against the back of the seat decreasing forward and backward movements

Many drugs have been advocated which either act as sedatives to the entire organism or effectively suppress the parasympathetic nervous system Hyoscine is no longer recommended since other drugs may now be used in which there is no hazard of respiratory depression from overdosage Dramamine 50 mg to 100 mg generally provides adequate protection for four to six hours Bonamine is more effective and less apt to produce drowsiness It may be administered as a 25 mg tablet at twelve hour intervals or in 50 mg dosage daily preferably about one hour before boarding the plane or ship The syndrome of motion sickness responds better to preventive medication but the drugs listed are helpful even after the symptoms have developed

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Electric Shock

Electric shock may result when the body becomes part of the path of flow of current between poles of different potential Broadly speaking alternating currents are considered much more dangerous than direct currents Fatal shock seldom results from contact with a direct current of less than 300 volts but the danger increases as higher voltages are attained Alternating currents if of few cycles (15 to 60) may cause death in well grounded subjects even at the 110 to 115 volts commonly used for home lighting but alternating currents of high voltage if of very high frequency may be handled with relative safety Maclachlan concluded from an analysis of 479 cases of electric shock that the severity of shock decreased or the success of resuscitative efforts increased as the potential of the circuit involved increased The resistance offered by the body as a conductor is a factor determining the severity of shock The resistance of dry skin is about 50 000 ohms per square centimeter varying in different parts of the body Moisture from sweating or wet clothing may lower the resistance to 1200 or 1500 ohms

If skin resistance reaches 1200 ohms an alternating current of 110 volts may prove fatal The nature of the "ground" may determine the seriousness of shock A subject immersed in a water filled bath might be killed by a current which could be tolerated under other circumstances The duration of contact is also of great importance since the severity of shock increases with an increase in the duration of contact Prolonged contact with low voltages is more likely than with high voltages for in the latter case the victim often falls clear aided by violent muscular contractions

Etiology The tendency of current of low voltage is to arrest the heart without affecting the respiration Alternating currents of low tension throw the heart in fibrillation High tension currents affect the central nervous system causing inhibition of respiration In one the result is heart death in the other respiratory paralysis It is inadvisable to generalize regarding the action of currents of moderate tension since many variable factors such as skin resistance grounding source voltage amperage duration of contact and kind of current determine the severity of the shock Much remains unknown concerning the mechanism and the effects of electric shock although the studies of Hoff and Nahum and their associates have contributed greatly to knowledge in this field

Morbid Anatomy Postmortem evidences of electrocution are variable Extensive charring may mark the points of entrance and exit of the current or the burns may be slight or absent The superficial destructive effects of direct currents are usually more extensive than those of alternating currents The blood is often dark and is rarely coagulated Minute hemorrhages and areas of destruction may be found in the brain and cord Reference should be made to the detailed reports of studies of the effects of electric shock upon the nervous system published by Morrison Weeks and Cobb

Symptoms Loss of consciousness momentary or prolonged and burns of varying degree usually accompany severe electric shock Death may be instantaneous or may result after some moments or hours Convulsions and priapism are common Those who recover from shock may suffer various after effects such as persistent muscular pain fatigue headache and nervous irritability Progressive loss of vision with opacity of the lens has been reported There are usually no permanent effects in those recovering from shock Because of the tendency to electrolysis of deep tissues and to the destruction of vessel walls the possibility of delayed hemorrhage must be kept in mind in the treatment of cases involving extensive burns

Prognosis In cases of cardiac failure due to ventricular fibrillation death must be expected Respiratory paralysis often responds to artificial respiration (In experimental animals however cardiac function has been restored after induced ventricular fibrillation Wiggers) Jex Blake considered death due to (1) prolonged muscular tetany resulting in asphyxia (2) ventricular fibrillation (3) respiratory failure through effects on the nervous system or (4) delayed effects of burns To these causes Kouwenhoven would add the more immediate effects of heat production and tissue coagulation

Treatment When the victim is freed from the current artificial respiration is the first measure necessary in the treatment of electric shock It should be instituted at once since a delay of even moments may result in death Although the "back pressure arm lift" method is rapidly replacing the "prone pressure" method either may be used and should be continued until rigor mortis sets in One patient at least was revived after 8 hours of effort There is some evidence that the return of normal respiration is hastened by the supplementary use of oxygen inhalations Counter shock or stimulation by mechanical means has been advocated but there is little or no reason to believe that it is of value Different authors following the experimental work of Levy who showed that ventricular arrhythmias leading to ventricular fibrillation and death could be induced by conditions which stimulated the heart and by equivalent conditions which removed or reduced depressing influences have called attention to the often fatal consequences of administering epinephrine and other stimulating drugs in electric shock Hoff and Nahum discovered that acetylcholine given to experimental animals protects them from ventricular fibrillation and death when they receive an electric shock of the strength which normally causes fibrillation of the ventricles The important clinical application which is suggested by these findings is obvious Spinal punctures as a hospital procedure in the after treatment for persistent headache or signs of cerebral pressure are of some value

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Diseases Due to Chemical Agents

Carbon Monoxide Poisoning

Carbon monoxide is a gas produced by the imperfect oxidation of carboniferous material and is probably the most widely distributed of toxic agents It is slightly lighter than air nonirritating colorless tasteless and in moderate concentrations odorless Ordinarily carbon monoxide does not appear in nature but may be encountered *in the home through accidental* leakage of manufactured gas from open burners and defective appliances and from incomplete combustion of various commercial gas products It is also encountered in many industries particularly in coal mining in the steel industry in gas manufacturing in processes utilizing gas heat and in connection with the use of explosives in confined spaces It is found in smoke in compartments which have been painted with oil paints and sealed and in the exhaust of internal combustion engines Many deaths have occurred in closed garages from motor exhaust gas and manufactured gas long has been used in suicide Coal gas contains about 16 per cent carbon monoxide blast furnace stack gas 28 per cent mine air after dust explosions 1 to 8 per cent and the exhaust from automobile motors about 7 per cent

Incidence Without doubt countless persons are daily affected to some degree by carbon monoxide There is a striking variation in individual susceptibility but no evident racial or sex predisposition Children are believed to be more susceptible than adults possibly because of their relatively greater respiratory exchange body weight considered Persons with cardiorespiratory disease are handicapped when exposed to carbon monoxide and the preexistence of certain nervous disorders may in persons poisoned result in aggravation of the nervous manifestations Some degree of acclimatization to carbon monoxide develops among those continually or frequently exposed to the gas and is shown in the lessening of symptoms during successive exposures to the same concentrations The possible explanation of this acclimatization is suggested by Killick as due to (1) a selective *activity of the alveolar membrane producing* either a secretion of oxygen from the alveoli into the blood or an excretion of carbon monoxide from the blood into the alveolvi or (2) removal of carbon monoxide from the blood by oxidative or other processes in the tissues

Etiology Carbon monoxide has an affinity for hemoglobin two hundred to three hundred times that of oxygen The reaction however is reversible and depends upon the relative tensions of carbon monoxide and oxygen in the alveolar air The gas is harmful in that it produces anoxemia Death is due to respiratory failure Though the problem has occasioned much study it has not been demonstrated that carbon monoxide is of itself specifically toxic Haldane suggested that it may poison a catalyst of oxidation

Poisoning depends not only upon the carbon monoxide content of inspired air but also upon the duration of exposure to the gas Particularly when exposed to moderate concentrations the blood does not attain the full saturation theoretically possible The maximum allowable concentration of carbon monoxide recommended by the American Standards Association is 100 parts per 1 000 000 parts of air by volume with atmospheric oxygen not below 19 per

cent by volume for exposures not exceeding a total of eight hours daily and 400 parts per 1 000 000 parts of air by volume for exposures not exceeding a total of one hour daily

Morbid Anatomy In the postmortem examination of victims of carbon monoxide poisoning there is often noted a bright cherry color of the blood Lining membranes are exceptionally red or show ecchymoses Particularly important are pathological changes in the brain characterized by hyperemia edema hemorrhage and diffuse degeneration Softening in the lenticular nucleus is regarded as the most typical lesion in carbon monoxide poisoning Yant and others found in dogs that the cells of the cortex the corpus striatum the dorsal motor nucleus of the vagus and the dorsal sensory areas of the medulla were especially involved Neurons were severely damaged showing disruption marked chromatolysis and other degenerative effects Though still a matter of some dispute the effects of carbon monoxide upon the nervous system are generally considered to be due essentially to asphyxia and not to immediate toxic action

Symptoms It has been observed by Sayers and others that the character and severity of symptoms under any degree of blood saturation depended largely upon the duration of exposure and the accompanying muscular activity and further that with a blood concentration resulting from long exposure to a low atmospheric concentration there were noted more severe symptoms and after effects than with a similar blood concentration resulting from a short exposure to a richer carbon monoxide mixture In general a concentration of 0 06 per cent or 6 parts of carbon monoxide in 10 000 parts of air produces headache within an hour and unconsciousness in two hours while 0 1 per cent carbon monoxide or 10 parts in 10 000 produces unconsciousness in a little more than an hour and may prove fatal in four hours

Carbon monoxide may kill with great suddenness Victims of mine dust explosions have been found in attitudes indicating that there was no warning of impending danger Though headache is usually the first symptom the onset may be insidious There have been many cases displaying a progressive muscular weakness without loss of consciousness but with disturbances of memory the victim passing into a rather insouciant oblivion from which he may emerge promptly or from which he may pass into full coma

The after effects in those recovering from acute poisoning are extremely varied Headache vertigo muscular weakness and nausea are common More rarely encountered are serious disturbances of memory vision hearing and speech or psychoses neuritis and paralysis Cerebral hemorrhage has been observed some days after apparent recovery A moderate polycythemia may persist for some time after all carbon monoxide has disappeared from the blood

Chronic poisoning by carbon monoxide is believed by many authors to be a clinical entity The alleged effects produced by repeated exposures to low concentrations of carbon monoxide are headache malaise and an ill defined debility However carbon monoxide is neither cumulative nor proved to be toxic and other causes should be sought for these and other subjective symptoms which persist long after the exposures to carbon monoxide have ceased

Diagnosis Absolute diagnosis is dependent upon the identification of carbon monoxide hemoglobin Hunter describes a simple test which may be used to prove the presence of carbon monoxide in the blood A greatly diluted solution of the suspected sample is compared with that of normal blood similarly diluted The latter is yellow whereas blood containing even a very small trace of carboxyhemoglobin is pink When the proportion of carbon monoxide in the blood is more than 40 per cent of saturation spectroscopic examination affords a confirmatory test Carbon monoxide indicators are now available on the market which indicate by direct reading of a meter the percentage of carbon monoxide present One of these is said to be sensitive to 0 005 per cent

Treatment Emergency treatment requires immediate artificial respiration if breathing has ceased preferably by the back pressure arm lift method It may be used advantageously for a short while even though the victim is breathing if asphyxia is marked The use when possible of an inhalator for the administration of oxygen is most desirable The inhalation of pure oxygen greatly accelerates the release of carbon monoxide freeing it about four or five times as rapidly as does air

Patients should not be permitted any physical exertion and should be kept warm Seriously poisoned patients after receiving emergency treatment may well be placed under observation in a hospital Medication and blood transfusions are rarely if ever indicated

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Silo Filler's Disease

In 1914 Hayhurst and Scott reported the death of four persons occurring apparently within about five minutes after their entering a partly filled silo Chemical analyses of the silo gases indicated an excess of 38 per cent carbon dioxide gas Under ordinary conditions about 0 03 per cent of the gas is found in the air Since that time numerous deaths—all during the autumn months—have been reported attributed to asphyxiation by carbon dioxide given off from fermenting ensilage

Another hazard in silo filling frequently referred to as a form of silo disease results from exposure to the oxides of nitrogen present in recently filled silos In 1956 Lowry and Schuman reported findings of *bronchiolitis obliterans* at autopsy in two persons who died after exposure Other similar cases have been recently reported So far there is no specific treatment for the resulting lung pathology The maximal permissible safe concentration for the oxides of nitrogen is 40 parts per 1 000 000 for an eight hour daily exposure

Prevention depends upon a wider recognition of the hazards involved and adequate ventilation People and animals should not be permitted to enter spaces adjoining a silo until ten days after the filling operations are completed

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Carbon Tetrachloride Poisoning

Definition Carbon tetrachloride (tetrachloromethane) poisoning may be defined as an acute subacute or chronic intoxication caused by carbon tetrachloride or its vapor It is characterized clinically by acute abdominal symptoms or pulmonary involvement as well as by serious injury to the liver and kidneys The clinical picture in some instances is dominated by pulmonary and renal injury either alone or combined with hepatic effects not evident in others signs of liver damage with evident jaundice and hepatic tenderness are outstanding In some persons gastrointestinal symptoms may be so severe as to lead to an early diagnosis of food poisoning or even of acute appendicitis A defatting of the skin with a resulting dermatitis may follow contact with carbon tetrachloride

Etiology Carbon tetrachloride is the most widely used of the halogenated hydrocarbon group of organic solvents It is encountered industrially as an extractant for fats and oils as a solvent in rubber cements textile soaps and other combinations and as a cleaning fluid and in fire extinguishers It is used in offices and homes as a dry-cleaning and degreasing agent Medicinally it is occasionally used as a vermifuge

Carbon tetrachloride alone or mixed with other solvents has been sold under many trade names such as Carbona Asordin Chlorasol (25 per cent carbon tetrachloride 75 per cent ethylene dichloride) Phoenipine Katarine Pyrene Spectral Tetra Tetracol Tetraform and no doubt others

Like other volatile solvents carbon tetrachloride exercises its effects only after absorption into the body The severity of the effects is generally proportional to the quantity absorbed Absorption may take place by inhalation of the vapor ingestion of the liquid or through prolonged or repeated contact of the liquid with the skin and mucous membranes The mode of entrance appears to have little or no influence on the results produced except that acute poisoning almost always follows exposure to an atmosphere highly contaminated with

vapor or to mistaken drinking of the liquid carbon tetrachloride Elimination takes place primarily through the lungs

The maximum acceptable concentration of carbon tetrachloride by the American Standards Association is 25 parts per 1 000 000 parts of air by volume corresponding to 0 157 mg per liter at 25° C and 760 mm of mercury for exposures not exceeding eight hours daily with the understanding that variations should fluctuate around 10 parts per million

Pathology In fatal poisoning which may follow a single exposure to a high concentration of the vapor damage to the liver kidneys heart adrenal glands and nervous system as well as a cerebral hemorrhage and bronchopneumonia with pulmonary edema may result Liver sections show a disseminated central necrosis with degenerative changes in the peripheral cells Petechial hemorrhages may be found on the surfaces of the lungs Areas of consolidation are not unusual The kidneys may reveal a lower nephron nephrosis Mallory describes the changes as like those in a kidney injured by transfusion crush or sulfonamides

Symptomatology There is considerable variation in the signs and symptoms of carbon tetrachloride poisoning depending upon the nature of exposure Acute intoxication results when an excessive amount of the vapor or liquid is absorbed into the body within a short period of time The first acute reaction is similar to that to chloroform—dizziness nausea vomiting backache malaise headache giddiness and unconsciousness—but is more toxic The narcotic effects are less marked than those of chloroform but the effects on the liver kidneys and heart are much more rapid *The effects on the heart are important* in acute poisoning because in addition to acting as a heart depressant there is a tendency to cause fibrillation Death may occur from circulatory or respiratory failure or the patient may recover within one or two days without any apparent after effects

Subacute poisoning usually resulting from prolonged or repeated exposure to an atmosphere containing a high concentration of the vapor but insufficient to cause loss of consciousness may cause headache nausea fatigue vomiting dizziness visual disturbances subconjunctival hemorrhage coughing and bleeding from the mucous membranes Some cases present hypertension Acute renal damage with albumin and casts in the urine or anuria may develop early and toxic hepatitis with a moderate degree of jaundice frequently occurs particularly in subjects who have ingested rather than inhaled carbon tetrachloride Pulmonary complications and coma may follow within a week after exposure and in some cases end fatally in one to two weeks

Chronic poisoning which is the result of daily exposures each small in itself over a longer period of time may be recognized by local symptoms of irritation of the mucous membrane of the eyes nose and upper respiratory tract The patient invariably complains of headache sleepiness fatigue and in more advanced stages abdominal pain edema and oliguria or anuria Jaundice may or may not be present Affections of the central nervous system have been observed

Diagnosis There may be confusion in the diagnosis of carbon tetrachloride poisoning because of the variability in its manifestations A history of absorption of an adequate quantity of carbon tetrachloride irrespective of the portal of entrance together with the symptoms and signs of the intoxication should make the diagnosis reasonably certain In general medical or hospital practice carbon tetrachloride poisoning is encountered most frequently after inhalation or skin contact with cleaning fluids in a closed room or after ingestion by alcoholics

Liver function tests kidney function tests roentgen findings in the chest and electrocardiograms should be *carefully* evaluated Serum bilirubin and nonprotein nitrogen are apt to be increased Albumin and casts in the urine are found in renal involvement There may be changes in the blood count but these do not dominate *the picture as they* do in poisoning by hydrocarbons of the benzene ring group of solvents

Roentgenographic findings in the lungs may vary from a mild prominence of linear markings to complete consolidation of one or more lobes of the lungs

Prognosis Although the fatality rate from carbon tetrachloride poisoning is low compared with the number of cases of intoxication reported there are a sufficient number of deaths to emphasize the need for precaution against carelessness in its use and *inadequate safety measures* In fatal cases nearly all deaths result from kidney and liver damage and occur three to ten days after exposure Most patients who survive the acute illness recover completely

Treatment Most important in any poison

ing is the prompt separation of the victim from the offending substance In instances in which the victim is overcome from inhalation of carbon tetrachloride vapors immediate removal to an uncontaminated area where he can rest quietly and be kept warm is imperative If breathing has stopped artificial respiration and the administration of oxygen are indicated Hot tea or coffee may be given as a stimulant if the patient is conscious but alcoholic stimulant or epinephrine is contraindicated in all stages of carbon tetrachloride poisoning When carbon tetrachloride is swallowed absorption from the stomach and intestines is rapid but early lavage or induced vomiting may be helpful This may be followed with Epsom salt (1 tablespoon) in water All contaminated clothing should be removed and affected skin areas should be washed thoroughly with a mild soap and warm water A mild ointment containing petrolatum or lanolin may be applied to the affected skin areas Any of the liquid carbon tetrachloride entering the eyes should be flushed out with copious quantities of water at room temperature

In the absence of specific therapy further treatment must be largely symptomatic varying with the individual symptoms and signs When kidney function is impaired the treatment is that of acute urinary suppression as outlined in the section on Diseases of the Kidneys Liver damage should be treated as described in the section on Diseases of the Liver

Prevention The measures at our disposal for the control of harmful concentrations of carbon tetrachloride as well as other solvent vapors in the plant atmosphere fall within three special fields safety engineering and medical Safety measures must be used against accidents or irregularities in operation Labels on cans and drums should indicate the hazardous nature of the substance and workmen should be instructed as to the dangers Personal protective devices such as protective clothing goggles and respirators—the latter are only for short exposures—should be provided when necessary Good housekeeping and sanitary facilities are essential and include segregation of processes care of spilled solutions receptables for soaked rags and ample general ventilation

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Benzene Poisoning

Benzene (benzol C_6H_6 to be distinguished from petroleum benzine) is with disturbing frequency the cause of serious and even fatal poisoning Benzene is obtained by the distillation of coal and the cracking of certain grades of petroleum It is used widely in the manufacture of rubber goods and artificial and patent leather in lacquers paints printing processes as a solvent for fats and greases and motor fuels and for a great variety of other purposes Commercial benzene contains a number of impurities such as thiophene and various homologues of benzene particularly xylene and toluene Extended investigation of the toxicity of such impurities has produced conflicting evidence but the preponderance of opinion favors the belief that they are not responsible for the effects generally attributed to benzene

Etiology Benzene poisoning is usually caused by inhalation of its vapor though it can be produced by skin absorption Although individual susceptibility to benzene varies greatly for reasons not determined the American Conference of Governmental Industrial Hygienists (1957) has adopted the threshold limit value of 25 parts benzene per 1 000 000 parts of air for the maximum average atmospheric concentration to which workers may be exposed for an eight hour working day without injury to health

Morbid Anatomy Most striking among postmortem findings are multiple hemorrhages throughout the body uncoagulated blood abnormalities of the bone marrow spleen and lymph nodes and evidences of secondary infection

Symptoms *Acute poisoning* may take place with great rapidity and death may ensue in a few minutes Beginning with sudden dizziness the victim may quickly show great muscular weakness and lapse through drowsiness into coma Tremors

delirium or convulsions are more infrequent There is often marked dyspnea with possibly a sense of constriction of the chest which may proceed to death from respiratory failure The pulse is small and rapid the skin pallid or cyanotic occasionally showing ecchymoses

Chronic poisoning or subacute poisoning is much more frequent and is manifested usually after days or months of exposure to benzene The early evidences of disease are commonly rather vague such as loss of appetite and weight headache vertigo and muscular weakness As the condition progresses pallor is marked and is associated with a true anemia Dyspnea and air hunger may be striking Convulsions and delirium are rare Abdominal pain and gastrointestinal irritation with nausea and vomiting are common Hemorrhages from the nose gums bowels kidneys and vagina as well as into the skin and mucous membranes are typical The urine often shows evidences of nephritis with casts albumin and blood Furunculosis may be encountered and possibly dermatitis related to skin contact with benzene

The blood picture may vary considerably from the so called classic changes Leukopenia neutropenia thrombocytopenia hypochromia eosinophilia and anemia may or may not be present The bone marrow may be aplastic or it may be affected or hyperplastic or leukemic Resistance to infection is lowered

Diagnosis The use of arbitrary criteria for diagnosis is not advocated The diagnosis cannot be made upon blood findings alone since these may simulate various blood dyscrasias The blood picture of agranulocytosis may be similar to that produced by benzene and the other well known causes of leukopenia A history of exposure to benzol should be the determining factor in the diagnosis of benzene poisoning The aromatic hydrocarbon detector developed by the Mine Safety Appliance Company is a useful apparatus for the field determination of benzene vapor

Prognosis Many seriously poisoned patients have died after several days or weeks others have recovered after prolonged illness The mortality among severe cases has in the past been about 50 per cent

Treatment Acute poisoning requires repeated washing of the stomach followed by the administration of 2 to 3 tablespoons of magnesium sulfate in 250 ml of water In instances of respiratory failure prompt artificial respiration is indicated The use of oxygen administered with an inhalator is advised Serious blood destruction and hemorrhage are best treated by blood transfusion possibly repeated many times The blood picture should be observed frequently Preparations of liver have been used to advantage Lane reports that corticotropin has been used successfully in some cases of aplastic anemia due to benzene Other treatment is symptomatic Because of lowered resistance to infection complications may appear such as pneumonia bronchitis and cystitis

Prophylaxis involves careful control of industrial processes in which benzene is used adequate ventilation the selection of healthy persons as workers with benzene and the periodic examination of persons exposed to the end that those even slightly affected may be removed

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Beryllium Poisoning

(*Berylliosis*)

Definition Beryllium poisoning or berylliosis is a general term which includes all those acute and chronic manifestations resulting from exposure to the fumes and dusts of beryllium salts and alloys In human beings the major clinical forms have been characterized chiefly by acute pneumonitis and chronic pulmonary granulomatosis Surface contact with the material may cause lesions such as conjunctivitis corneal ulcer dermatitis on the hands arms face and neck skin ulcer or granuloma and subcutaneous granuloma

Pathology In the acute form of the disease the lungs present a picture of bilateral diffuse pneumonitis with pronounced intraalveolar and interstitial exudates The air

spaces are filled with plasma cells lymphocytes and mononuclear phagocytes attended occasionally with edema and hemorrhagic extravasation These may infiltrate the smaller blood vessels and bronchioles There is an early proliferation of fibroblasts Unlike cases of acute chemical pneumonitis from other causes polymorphonuclear leukocytes are relatively few

The chronic form of the disease is characterized by marked emphysema and a bilateral diffuse granular or nodular infiltration scattered through the lung fields The normal structure of the lungs may be altered and is often obliterated by these changes

The nodular granulomatous lesions are located in the thickened walls of the alveoli and in the fibrous tissue around the bronchi and blood vessels The central core of the lesions consists of fibrinoid material lymphocytes plasma cells large mononuclear phagocytes and giant cells of the Langhans type The peripheral zone consists of fibrous tissue infiltrated with small round cells Giant cells may or may not be present Conchoidal bodies are present in most cases

The mediastinal and axillary lymph nodes are infiltrated in some instances by a similar granulomatous process Liver involvement also has been observed The skin and subcutaneous tissues may be the sites of granulomas following accidental introduction of beryllium compounds

Morbid Physiology The extensive changes in the parenchymal lung tissue and associated thickening of the walls of the alveoli interfere with the exchange of gases in the lungs Alveolar capillary block develops with uniform reduction in lung volume hyperventilation well maintained maximum breathing capacity arterial oxygen unsaturation (particularly on exercise) and normal or even low carbon dioxide levels The anoxemia is due to impaired diffusing capacity of the lungs for oxygen

Symptoms The acute form of the disease develops usually after a relatively short period of exposure The symptoms may appear insidiously or suddenly beginning with an acute irritation of the upper respiratory tract cough which is often nonproductive dyspnea substernal discomfort or pain anorexia weakness and weight loss The objective signs reveal a thin anxious person with little or no elevation in body temperature There is usually some swelling and redness of the mucous membranes of the nose and throat Cyanosis is evident in severe cases Rales may be detected in both lung fields The illness may subside within a few weeks or extend into several months

The symptoms and signs in chronic cases appear insidiously and include exertional dyspnea weakness irritative cough and weight loss The onset of symptoms may be delayed for periods of several weeks to five or six years following termination of exposure As the disease progresses the symptoms become more localized and intense There is a progressive loss in weight and variable degrees of respiratory distress The patient appears nervous and complains of pain in the chest and abdomen weakness and fatigability Cyanosis and clubbing of the nails may be present The pulse rate is usually increased and definitely accelerated in cases of cyanosis The blood pressure usually drops during the course of the disease Rales and loss of resonance have been observed Reduction in vital capacity may become marked as the disease progresses The duration of the disease is prolonged usually for a period of several months

Diagnosis The diagnosis is made after a careful evaluation of the occupational history type of onset and clinical manifestations roentgenographic characteristics and chemical findings of beryllium in tissues obtained by skin biopsy or in the urine

The occupational history should include all occupations in which the patient has been engaged and the duration of employment in each as well as all obtainable information on the amount and kind of dust and fumes to which he has been exposed and the extent to which protective devices were used The inhalation of beryllium dust after breaking fluorescent lamps may occur and this possibility should be inquired into when there is a history of exposure prior to 1949 Beryllium phosphors have not been used in the manufacture of fluorescent bulbs since that date

In roentgenographs of the lungs in acute pneumonitis a diffuse haziness may be noted two to three weeks after the early symptoms of the disease There is usually prominence of the peribronchial markings and irregular opaque shadows suggestive of pulmonary edema followed by discrete small or large conglomerate nodules scattered throughout both lung fields Clearing of lung fields occurs usually after one to four months

The roentgenographic changes in the chronic disease are characterized by small discrete stippling and fine nodulations scattered throughout both lung fields re

sembling the shadows cast in miliary tuberculosis in sarcoidosis and in early uncomplicated silicosis As the diseases progresses confluent nodular shadows with emphysematous spaces between appear throughout both lung fields There may be an accompanying enlargement of the hilar lymph nodes

Prognosis The course and prognosis of beryllium poisoning depend largely upon the form of the disease The mortality rate is low in the acute form Only occasionally has death occurred early in its course The transition from acute pneumonitis to chronic pulmonary granulomatosis has so far rarely been observed Machle and his co workers however report that an attack of acute disease has been followed two years later by the onset of chronic beryllisosis and gradations of intermediate degree occur

The chronic course of the disease is one of protracted convalescence in a few and gradual progression and eventually death in many Machle reports a fatality rate of 20 per cent in his series of cases Cutaneous lesions do not readily heal unless all particles of the beryllium material are removed and granulomas of the skin are excised

Treatment In the absence of specific therapy in the acute and chronic pulmonary forms of the disease the treatment must be largely supportive Enforced bed rest in early and severe cases is indicated Oxygen therapy is required to overcome cyanosis and dyspnea and to prolong life Cortisone and ACTH have been shown to induce striking improvement in pulmonary function with marked clinical improvement in a number of patients with pulmonary granulomatosis Antibiotics may be of value in preventing secondary infections

Dermatitis and conjunctivitis although severe at times tend to clear up after removal from work The application of a mild antipruritic or antihistaminic ointment may aid in the treatment of affected skin areas and a soothing antibiotic ophthalmic ointment may be applied in cases of conjunctivitis Cutaneous ulcers are best treated by scraping away the base of the ulcer with a curet Cutaneous and subcutaneous granulomas should be widely excised

Prevention Prevention consists in both medical and engineering control A periodic checking of workers possibly exposed to beryllium containing fumes and dusts is a valuable health measure in detecting early cases A monthly check of each workers body weight for evidence of persistent loss and interrogation as to symptoms such as cough anorexia and fatigue is desirable When suspicion points to possible disease of the respiratory system a roentgenogram of the chest should be made All workers incurring breaks in the skin should be required to seek immediate treatment so that the medical attendant can remove all particles of beryllium compounds in the wound

Good engineering practice consists in meticulous housekeeping and systematic determinations of the beryllium content of air at breathing levels of the workers Until safe limits of concentrations are determined every effort should be made through engineering control methods to prevent beryllium containing fumes or dusts from escaping into the atmosphere

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Mercury Poisoning

Mercury has long been used in the arts and in medicine Paracelsus (1493–1541) advocated its use for the treatment of syphilis

ACUTE POISONING

Etiology Acute poisoning is usually caused by ingestion of bichloride of mercury accidentally or with suicidal intent The absorption of mercury administered therapeutically by mouth injection inunction or in vaginal douches may produce a mild acute or subacute poisoning as does rarely an industrial exposure to massive doses of mercury vapor Ingestion of 0 1 gm of mercuric chloride may result in acute poisoning although usually 1 gm or more is required to render the condition serious Mercury is quickly absorbed from the stomach and after brief storage in the liver is widely distributed

Morbid Anatomy In patients dying within 24 hours after ingestion of mercury there is observed marked gastritis and possibly some nephritis Patients dying within two to seven days after ingestion show a necrotic nephrosis and marked colitis Those dying after one week show a tendency toward healing of the gastric and renal lesions but a severe gangrenous colitis

Symptoms The onset is usually rapid within a few minutes after ingestion abdominal pain develops especially in the epigastrium This is fortunately in most cases associated with vomiting and rejection of part of the ingested poison There is a metallic taste and often a marked stomatitis and congestion or even ulceration of the pharynx and esophagus The vomitus may early contain blood streaked mucus Stools are loose and bloody There may be prompt collapse and in exceptional cases delirium and convulsions Examination of the blood during the first few days shows blood nitrogen increased the blood chlorides reduced and the alkali reserve lowered When the intoxication is not promptly fatal signs of gastrointestinal inflammation and striking evidence of injury to the kidneys usually continue Albumin casts and blood appear in the urine a few hours after ingestion of the poison and gradual suppression of the urine and anuria may be noted

Diagnosis It is important to ascertain with certainty that mercury has been ingested Some of the new methods for the determination of mercury are the electrolytic dithizone selenium sulfide spectrographic and photoelectric Spectro-analysis has become a valuable diagnostic aid Small amounts of mercury have been found in the urine and stools of apparently normal healthy persons

Prognosis If mercurial salts are vomited within fifteen minutes of ingestion the patient usually recovers The frequent estimation of blood nonprotein nitrogen is of aid in prognosis The majority of deaths occur within the first two or three days The mortality among proved cases may run over 40 per cent though with prompt and thorough treatment in hospital it should be less than 10 per cent If death is not caused by shock or severe gastroenteritis it is usually attributable to kidney damage

Treatment Emergency treatment may include induced emesis and gastric lavage or treatment of shock The treatment described by Weiss is devised to overcome the effects produced by the poison rather than to provide an antidote to mercury It may be outlined as follows

The stomach is immediately washed with a saturated solution of sodium bicarbonate the operation being continued until the washings are clear At least 2 liters of the solution should be used

Lavage with 250 ml of a 5 per cent solution of sodium formaldehyde sulfoxylate has been recommended particularly in cases seen early Before withdrawing the stomach tube 6 ounces of a saturated solution of magnesium sulfate are administered A soapsuds enema is then given

From the onset a beverage made by dissolving 4 gm (1 teaspoonful) of potassium bitartrate and 2 gm (½ teaspoonful) of sodium citrate in a glass of water orangeade or lemonade is to be administered six to eight times daily Weiss has seldom used rectal irrigation or hot packs He permits a liberal diet after diarrhea ceases

Dimercaprol (BAL) has also been used with success in mercury poisoning The initial dose should be 5 mg per kg (approximately 300 mg) intramuscularly followed in one or two hours by a dose of 2 5 mg per kg After a lapse of two to four hours a second dose of 2 5 mg per kg should be given within the first twelve hours of therapy On the second day two 2 5 mg per kg doses may be administered It should be emphasized that the successful treatment of arsenic or mercury poisoning with dimercaprol depends on the institution of treatment at the earliest possible moment before irreparable tissue damage has occurred and on the use of adequate amounts of dimercaprol at frequent intervals

Renal damage with suppression of urine is usually a major problem in acute mercury poisoning For management of urinary suppression see page 1064

SUBACUTE POISONING

Subacute poisoning is ordinarily caused by the excessive therapeutic use of mercury The common symptoms—salivation gingivitis and diarrhea—subside upon withdrawal of the drug

INDUSTRIAL POISONING

Industrial mercury poisoning is almost invariably a chronic intoxication resulting from the inhalation of volatized mercury for a long period One milligram of mercury per 10 cubic meters of air has been accepted by the American Standards Association as the maximum allowable concentration for work places Dublin and Vane list about 100 occupations in which mercury may be a hazard The most hazardous trades are the production of mercury and its derivatives the manufacture of scientific apparatus (thermometers and barometers) the extraction of gold and silver

by amalgamation the application of anti fouling plastic paint for the protection of hulls of warships against the growth of aquatic life and the preparation and handling of the *fulminate of mercury* as a detonator of explosives Since the recent discovery of a substitute for mercury in the treatment of fur certain states by agreement with the manufacturers of felt hats have issued regulations prohibiting the use of mercurial carrot in the preparation of hatters fur or the use of mercurial carroted hatters fur in the manufacture of hats

Symptoms Chronic mercurialism has various manifestations not all of which may be observed in any one case The most typical symptoms are included in the first three of the following groups

1 *Stomatitis* salivation a metallic taste reddish brown discoloration of the buccal mucosa gingivitis loosening of the teeth and occasionally a marking of the gums similar to the lead line

2 *Erethismus mercurialis* a peculiar psychic disturbance characterized by ready excitability and a strange shyness in the presence of strangers insomnia headache vertigo mental depression and dullness and rarely hallucinations

3 *Tremors* of the orbit lips tongue fingers and limbs These are usually moderately fine at first but at intervals become a coarse jerking They may become severe and in rare instances involve contractions of the limbs of such violence as to require restraint The tremor is intentional and subsides during rest Under observation it may increase and diminish rhythmically recurring When it is marked the patient may require assistance in eating and in other activities Weakness of both the flexor and extensor muscles of the hand and forearm has been reported but marked paresis is rarely if indeed ever caused by mercury Polyneuritis is said to result occasionally from exposure to mercury No ataxia occurs and reflexes are not notably affected

4 *Albuminuria and High Blood Pressure* While the severe nephritis associated with acute mercurial poisoning is not associated with the chronic type these symptoms appear with such frequency as to warrant the belief that the kidneys are usually involved in chronic poisoning

5 *Loss of appetite indigestion and diarrhea* are occasionally observed There is loss of weight in severe cases The blood is normal except for a moderate secondary anemia

6 *Dermatitis* characterized by erythema and desquamation is not uncommonly produced by contact with mercuric chloride or even by ingestion of mercury In susceptible persons fulminate of mercury produces severe *dermatitis* Punched out and penetrating ulcers may develop about the fingernails and knuckles The conjunctivas and the mucous membranes of the mouth nose and larynx are often affected

Prognosis There is apparently no acquired immunity to mercury The severity of symptoms is usually determined by the length and degree of exposure to the poison Though most severe symptoms tend to decrease when the subject is removed from contact with mercury such manifestations as erethism and tremor may persist for a long time

Treatment should eliminate the metal through the bowels kidneys and skin In acute mercury poisoning BAL has been effective For the dosage of BAL the reader is referred to the section on Arsenic Poisoning

Mercury dermatitis may be prevented and to some degree relieved by application of a 10 per cent solution of sodium hyposulfite A 2 per cent solution may be used as a wash for conjunctivitis

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Arsenic Poisoning

Arsenic poisoning is usually the result of exposure to one of the oxides of arsenic such as arsenous acid (As_2O_3) or to arsenical salts such as emerald green (aceto arsenite of copper) or lead arsenate *Arseni*

uretted hydrogen (arsine AsH_3) is highly toxic but produces effects different from those of arsenic salts

Incidence Most industrial arsenic poisoning is seen in workmen engaged in extracting white arsenic (As_2O_3) from cobalt and arsenical pyrites in chemical works glass making and cadmium plating in agricultural spraying and dusting in the use of sheep dip or in handling skins treated with arsenic Poisoning has been reported from the use of the organic arsenic compounds from fruit sprayed with arsenic and from certain cosmetics and proprietary remedies

Arsine is produced when an acid and a metal either or both containing arsenic are brought into contact with a resulting liberation of nascent hydrogen which combines with arsenic to form the toxic gas Poisoning has occurred in chemical and galvanizing works in submarines because of arsenic in storage battery plates or acid on ships carrying ferrosilicon which in contact with air and moisture tends to decompose and liberate arsine and in the preparation of hydrogen for balloon inflation

Etiology Arsenic oxide and the salts are local irritants to the skin and the mucous membranes of the mouth and respiratory passages inhalation or ingestion of them produces local and systemic changes Acute poisoning is usually due to the use of arsenic with suicidal intent One grain (65 mg) of white arsenic has proved fatal Though the normal therapeutic dose of this substance is 2 mg the "arsenic eaters" of Styria can safely take over 400 mg twice a week

Arsine is primarily a hemolytic agent The inhalation of the gas over a period of several hours in a concentration of 30 parts per 1 000 000 will produce poisoning and the lethal dose as variously stated ranges from 100 mg to over 500 mg There is apparently marked individual susceptibility

Morbid Anatomy Delepine reported that after poisoning by arsenic trichloride there is found granulofatty degeneration of the heart liver kidneys pancreas and gastric and duodenal glands After death from poisoning by arsine the liver has been found to be large and edematous with some evidence of fatty degeneration the kidneys large and the renal epithelium degenerated and necrotic Ecker found significant alterations in the nervous system marked by alterations in the ganglion cells and by regions of perivascular necrosis

Symptoms Arsenic oxides or salts as dusts produce superficially a dermatitis or even ulceration about folds of skin as in the axillae or about the scrotum Increased pigmentation may be noted about the axillae the nipples the eyelids and on the neck Keratosis of the palms and soles may develop after prolonged ingestion of arsenic and skin cancer has been reported to follow the use of the drug The causal relation of arsenic to skin cancer is much disputed The septum of the nose in some cases is perforated Other symptoms are edema of the lids coryza pharyngitis and laryngitis With more serious poisoning vomiting abdominal pain and diarrhea may be marked A peripheral neuritis with pronounced paresthesia is moderately common Paralysis similar to that produced by lead may result from the absorption of arsenic the legs being more notably affected than the arms Tendon reflexes are diminished or lost Diffuse cerebral symptoms such as headache vertigo fatigue drowsiness and impairment of mental activity may result from chronic absorption

Poisoning by arsine is manifested usually three to six hours after the gas is inhaled by malaise vertigo weakness headache nausea and vomiting There may be abdominal pain and diarrhea A few hours later hemoglobinuria or hematuria and albuminuria are noted The pulse may become rapid and feeble and the respiration increased Within a day or two jaundice and a coppery cyanosis may be observed Oliguria may develop The red blood cells and hemoglobin are much reduced In very severe cases there is a high color index and evidence of extreme blood destruction as well as of regeneration The leukocytes are ordinarily not involved though in some cases there is a slight leukocytosis There develops rarely after several weeks a transitory toxic polyneuritis with pain or anesthesia but no motor involvement

Diagnosis of arsenic poisoning is facilitated by careful inquiry into the nature of the patient s work and by chemical analysis of the urine hair and nails In connection with such analyses it should be noted that normal" arsenic frequently has been found in the hair nails and excreta of persons not known to be exposed to arsenic

Prognosis Industrial poisoning by arsenical oxides or salts is rarely fatal Manifestations of the disease may persist for weeks or months Poisoning by arsine if severe is usually fatal within about a week death being due essentially to blood destruction

The mortality is approximately 30 per cent Serious damage to the kidneys is almost inevitable and impaired renal function complicates recovery Convalescence is slow

Treatment In acute cases of arsenic poisoning remove material promptly by gastric lavage using warm water or a 1 per cent solution of thiosulfate The administration of absorbent charcoal and of cathartics has been suggested Also the administration of BAL (British anti lewisite antidote to the arsenical blister gases) may be helpful It has been suggested that 3 mg of BAL or dimercaprol per kg or a 10 per cent solution in oil be given intramuscularly every four hours for the first two days four injections on the third day and injections twice daily thereafter for ten days or until complete recovery Subcutaneous injections of morphine (15 mg) may be necessary to relieve pain Dehydration may be treated by intravenous infusion of 5 per cent glucose

In chronic poisoning the promotion of elimination through the kidneys and bowels is recommended

In poisoning by arsine oxygen should be promptly administered and the inhalations prolonged Transfusion may be necessary In the few cases of arsine poisoning in which BAL was given the results proved generally unsatisfactory Pinto and others found that it neither stopped nor prevented the destruction of red cells

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Metal Fume Fever

It was generally believed by earlier observers that the syndrome known as metal fume fever as well as so called smelter shakes brass founder s ague zinc chills and brass poisoning was due to zinc inhaled as a metal oxide fume The chief industries involved were brass or bronze foundries zinc ore smelters and those engaged in welding zinc and its alloys in brazing metals and metallizing with zinc Later studies have shown that the fumes of other metallic oxides antimony arsenic manganese lead copper beryllium magnesium and probably others will produce similar episodes of chills and fever

The symptoms usually occur several hours after exposure and are aggravated by chilling of the body The patient may complain of dryness of the throat some tightness in the chest followed by a dry cough and occasionally nausea and vomiting The fever may rise to 102 F sometimes higher *The patient usually recovers* on the day following the chill No fatalities have been reported

Prevention depends upon adequate engineering and medical programs During an eight hour day exposure should not exceed 15 mg per cubic meter of air Suitable exhaust ventilation of the work area is essential

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Lead Poisoning

Definition Lead poisoning *is a systemic* intoxication which may occur *when the* concentration of lead within the tissues reaches or exceeds a certain critical range The intoxication often spoken of as chronic largely because of the length of time which may be required under given conditions of exposure and absorption for the concentration of lead in the tissues to reach the critical range occurs usually as an acute episode of illness of fairly sudden onset Such illness does not ensue necessarily when the critical concentration of lead in the tissues has been reached or exceeded *The illness is initiated by obscure* factors which effectuate the toxic reaction

Etiology Lead poisoning in the adult in the United States is essentially occupational in origin Occasional cases are seen among persons who have been using water conveyed from a spring or well through lead pipes to a house in a rural area

Rarely poisoning has resulted from ingestion of lead compounds in solution or in the form of paste or powder and from the absorption of lead from fragmented lead shot or bullets when these have been lodged within a joint where the combination of a fairly extensive surface mechanical erosion and local tissue reaction (usually in association with infection) has accelerated greatly the absorptive process As a rule shot or bullets merely embedded in the tissue or encapsulated are inert and harmless

Occupational lead poisoning occurs in association with a variety of routine procedures in which metallic lead alloys containing lead in significant concentration and other compounds of lead (such as paints of high or intermediate lead content on metallic or wooden surfaces) are heated to temperatures sufficiently high to produce lead fume or lead vapor (temperatures above 1000 C in the case of metallic lead) The heat may be applied to a mass of metal as in a furnace or melting pot or locally as by a blowtorch an electric arc or an oxyacetalene burner Procedures of this type result in contamination of the atmosphere of workrooms with finely divided lead or its compounds and when the concentration of respirable lead or lead compounds in the atmosphere breathed regularly or frequently exceeds 0 2 mg per cubic meter for months or years cases of lead poisoning occur

Other industrial operations of a wide variety *e g* *spraying stirring skimming* grinding scraping abrading conveying and shoveling are concerned at some stage with metallic lead or lead compounds in a physical state that is conducive to the dispersion of fine particles of mist or dust into the air and to the rapid or gradual settling out of all but the finely dispersed particles upon flat surfaces within the vicinity of the operations The contaminated air is a source of respiratory exposure to all unprotected persons in the area involved and the settled dusts constitute a source of further contamination of the atmosphere whenever mechanical procedures or air currents redisperse them

Hazardous situations with respect to lead have been eliminated from many plants and processes in recent years and other unrecognized hazards have been introduced so that no industry *per se* is either dangerous or free of danger

Lead and its inorganic compounds are absorbed into the body by way of the respiratory and alimentary tracts None of the inorganic compounds is absorbed to any practically important extent through either the unbroken or abraded skin Certain oil soluble organic compounds of lead on the contrary are readily absorbed through the unbroken skin Of these only tetraethyl lead has any importance in present-day industry and its only significance as a source of cases of lead poisoning arises in connection with the manufacture of tetraethyl lead and in the handling of mixtures or solutions in which tetraethyl lead is present in high concentration Commercial leaded gasoline in which only minute concentrations of tetraethyl lead are found is not a source of tetraethyl lead poisoning in its ordinary handling and use as motor fuel except under the peculiar conditions associated with the cleaning and repairing of large gasoline tanks in which the gasoline has been stored for considerable periods of time

The emphasis above upon the dispersion of lead in the atmosphere and the general preoccupation of industrial hygienists with the contamination of the atmosphere with lead compounds tend to minimize the importance of the absorption of lead from the alimentary tract However lead poisoning can result from alimentary absorption alone and is the usual mode of absorption in children Moreover the size of the particles dispersed in the air determines to a very considerable extent the fate of lead compounds that enter the respiratory tract Many of the particles ranging in size from somewhat more than one micron upward increasingly as they increase in size are collected in the upper respiratory tract and as great a proportion as 75 or 80 per cent of those which enter the nares may be swallowed Inasmuch as the ingestion of one milligram of lead per day in addition to that which occurs normally in food and beverages results in the slow but progressive accumulation of lead in the body it is evident that the quantity of lead which reaches the alimentary tract in connection with respiratory exposure to lead is often a highly significant factor in the total absorption of lead under these conditions

The absorption of toxic amounts of lead by children is usually an expression of the presence in the environment of dangerous quantities of readily accessible paint of significant lead content (in excess of 1 per cent of lead in the dried paint) The usual source of dangerous quantities of lead is found to be the painted and repainted surfaces of woodwork *e g* baseboards windows and window sills cribs play pens

and plaster walls Other sources of lead poisoning in infancy and childhood have been nipple shields small toys made of metallic lead or its alloys cosmetic powders and hair dyes

Pathology and Chemistry After the absorption of its inorganic compounds lead is widely distributed in the tissues of the body Within a period of about two weeks after the absorption of a single dose of significant size the distribution assumes a *pattern in which the skeleton contains 90* per cent or more of the lead in the body but the quantities found in the viscera at all times are appreciable those in the liver and the blood being the largest of these Inasmuch as the average normal adult takes in somewhat more or less than 0 4 mg of lead per average day in food beverages and respired air the stream of lead absorption into and through the tissues of the body is always a factor in the distribution but the pattern of the distribution in the tissues and urine is one of the most constant and stable of normal human metabolic phenomena When the rate of absorption of lead increases coincident with abnormal exposure the pattern of distribution is changed but little but the quantities involved increase in rough proportion to *the rate of absorption Under appropriate* conditions of abnormal exposure the lead content of the skeleton may come to be ten to thirty times its normal level *i e* between 1 0 and 2 0 mg per 100 gm of fresh bone while that of the liver is likely to be elevated tenfold or more that in the blood eight to twentyfold and that in the urine ten to twentyfold It is usually impossible to establish even the approximate facts with reference to the true alimentary excretion of lead in any other than balance observations of some weeks duration since the large proportion of the lead ingested daily and passed unabsorbed through the tract masks that which is actually excreted from the tissues For this reason the alimentary excretion need not be referred to beyond stating the fact that as a true excretion it is often negligible and is rarely more than two or three times as much per day as is that excreted in the urine Under normal circumstances the concentration of lead in the central nervous system rarely exceeds 0 08 mg per 100 gm of fresh tissue but in fatal encephalopathy it ranges from about two to more than five times the normal

There are no entirely characteristic changes in the tissues in lead poisoning A variety of gross and microscopic lesions are found however in association with varying types and degrees of severity of lead poisoning Of these the most nearly definitive are (1) the degenerative lesions of the neuromuscular apparatus involving the extensor muscles of the extremities and the associated *peripheral nerves and neu*rones (2) the cerebral edema of encephalopathy with or without obvious and nonspecific damage to nerve cells (3) basophilic stippling of the erythrocytes in the *peripheral blood* (4) the deposition of black lead sulfide in gingival margins that are the site of inflammatory changes the so called lead line and also at times in the mucosa of the large intestine (5) and the changes in the metaphyseal areas of the long bones of children which are visible as linear areas of sharply increased density in roentgenograms and are demonstrable as regions of unusually dense trabeculation and tissue reaction on microscopic examination These "lines are not specific for lead nor is the x ray shadow due to the elevated concentration of lead *in these areas but to the dense local struc*ture of the bone While vascular injury with or without petechial or even gross hemorrhage (retinal hemorrhage for example) occurs occasionally in lead poisoning *it has no special or differentiating site* or character

Whether intoxication with lead depends upon the presence of ionic lead or an ionized radical containing lead in the affected tissue or tissues as *differentiated* from lead which is held in an nonionized or weakly ionized combination in the tissues or whether some other type of biochemical mechanism is involved in the process is not known From the aspect of chemical pathology an inhibition of the maturation cycle of hemoglobin caused by the presence of sufficient concentrations of lead results in an increase in certain porphyrins in the circulating blood and in the urine of which coproporphyrin III is the most significant The appearance of coproporphyrin III in the urine in sufficiently elevated concentration is perhaps the most nearly specific of all the abnormalities associated with the absorption of dangerous quantities of lead The finding of abnormal quantities of lead is of course the only truly specific bit of evidence but is not *per se* an indication of disease

Symptoms and Clinical Pathology In the adult the commonest expression of lead poisoning is that of acute bouts of mid abdominal pain which may come and go or may persist with varying *intensity at*

its worst causing the patient to writhe "coiled up" in a cold sweat from time to time because of acute enteric spasms There may be little prodromal indication of illness but it usually follows in the wake of a period of increasing constipation often becoming intractable in association with loss of appetite particularly at the beginning of the day and discomfort on eating The patient usually complains of a foul rarely metallic taste sometimes of nausea with or without vomiting and of weakness which is occasionally extreme but almost always strikingly out of proportion to his apparent strength The disease is essentially afebrile but there may be a mild elevation of temperature when bouts of colic are severe There is pallor and although the inevitable loss of weight may be mild the patient appears debilitated In some patients constipation and other digestive disturbances constitute the chief complaints and they are worn down by lack of sleep and weakness at least in part because of reduced food intake

In another form of the disease the complaints are referable chiefly to the neuromuscular system with the pain of muscular hypertonus in the legs especially the calves and weakness or paralysis of the extensor muscles of the arms particularly of the forearms or hands The latter is rarely the first manifestation of the disease being usually an expression of fairly prolonged exposure to highly hazardous occupational conditions It is also common to find that the patient who is suffering from this form of lead poisoning has had one or several previous bouts of colic

The cerebral manifestations of the disease develop suddenly—in adults usually as a result of severe occupational exposure especially to lead fumes The onset may be announced by a convulsion or the patient may develop a severe headache and become confused disoriented and negativistic This condition may progress to a state of unresponsiveness to stimuli which may persist for some days with little change or may go on into deep coma On the other hand the initial cerebral disturbance may clear abruptly or in a few days leaving little more evidence of cerebral involvement than that associated with a bad "hangover"

The two expressions of lead encephalopathy referred to above so different in their duration and apparent significance are probably differently mediated toxic effects of lead although the mechanisms involved are still conjectural The form of encephalopathy seen in infancy and childhood bears more resemblance to the severe than to the mild forms of adult encephalopathy especially in respect to its poor prognosis Its onset is usually characterized by convulsive seizures and from its onset until shortly before a fatal termination its manifestations are more those of meningeal irritation and cerebral excitation than of depression Like adults children show evidence of lead intoxication other than encephalopathy The milder forms of the disease in children appear to occur with less relative frequency than the severe form but this may be more apparent than real

Tetraethyl lead poisoning deserves special consideration because it is always primarily an acute intoxication of the central nervous system When tetraethyl lead has been absorbed into the body in sufficient concentration the response is always the same in type with some variation in degree This intoxication appears as a fairly characteristic mental disturbance which in the more severe cases develops in intensity with somatic manifestations of nervous excitation until the cerebral mechanisms mental and motor alike come to be involved in an outburst of activity of maniacal intensity Yet when the patient survives this storm he returns ultimately to a normal state without permanent sequelae Fatal encephalopathy due to tetraethyl lead like the encephalopathy of infancy and childhood is associated with highly abnormal and apparently definitive concentrations of lead in the brain In view of the lack of sequelae it appears that the disorder in the brain is primarily functional and is mediated by this chemical agent

Diagnosis The diagnosis of lead poisoning is made on the basis of characteristic symptoms and signs or those compatible with lead intoxication together with reliable evidence of the absorption of toxic quantities of lead and in the absence of other disease processes giving an alternative basis for the disease picture *The history of exposure is but a clue to be investigated and discarded or substantiated as facts are gathered by more appropriate methods*

Because the symptoms of lead intoxication are likely to be more striking than the physical signs the former must be considered with great care both as to their meaning and their validity The patient s opinions about the nature of lead poisoning and his apprehension concerning the effects

of the disease upon his future health and upon his present and future economic status must be appraised carefully particularly because problems of compensation often become a major consideration

The important objective manifestations of lead intoxication some combination of which may be seen in the usual case include severe cachexia and weakness enteric colic without significant fever leukocytosis or evidence of peritoneal inflammation *weakness or paralysis with or without* atrophy and without sensory changes of the extensor muscles of one or more of the extremities involving the lower extremities only rarely in the adult toxic encephalopathy to be differentiated from infectious or viral encephalitis or hypertensive encephalopathy

All but the most typical and uncomplicated cases of lead poisoning require diagnostic elucidation by means of either presumptive or specific and incontrovertible evidence that abnormal and dangerous quantities of lead have been absorbed by the patient Such evidences of themselves with the exceptions that will be indicated are not signs of intoxication but of absorption Of these only one can be observed in the course of the usual physical examination—*the lead line of blue black deposit* in gingival margins that are the site of an associated gingivitis This must be differentiated from deposits of other black metallic sulfides from the normal gingival and buccal pigmentation of dark skinned races and from the purplish blue margins of gingival congestion Since a "lead line may occur when the lead content of the tissues is insufficient to cause illness it must be considered as evidence of abnormal but not necessarily toxic absorption of lead

Other presumptive but nonspecific laboratory evidence includes the following roentgenographic demonstration of the presence of opaque substances in the alimentary tract of the small child from his having swallowed bits of paint or fragments of painted objects the presence of the lines of metaphyseal density in the bones of young children microcytic hypochromic anemia and basophilic granulation of the erythrocytes and the finding of abnormal concentrations of coproporphyrin III in the urine The nonspecific anemia of lead intoxication is not always demonstrable and the stippling of the erythrocytes is in no wise differentiable from that found in a variety of other diseases The finding of coproporphyrin III in abnormal quantities although in all probability one of the earliest signs of a toxic effect following the absorption of lead is lacking in specificity and is too variable to be more than a contributory bit of diagnostic information The results of these procedures are of value when *combined with other* satisfactory clinical appraisals of a patient and his exposure to lead and may establish a body of circumstantial evidence that is entirely convincing Nevertheless a conclusion *arrived at by these nonspecific clinical* and laboratory methods may not be valid especially in children

The procedure of choice in establishing the extent of the patient s absorption of inorganic lead is that of a precise determination of the lead content of his whole blood The same purpose can usually be accomplished by the determination of the general rate of excretion of lead in the urine In patients with intoxication due to tetraethyl lead only the analysis of the urine is helpful since tetraethyl lead and its major degradation products are not taken up by *the erythrocytes* Because of the variability of the urinary excretion of lead and the frequency of contamination of the urine during its collection the sampling and analysis of the urine are considerably *more troublesome than the cor*responding procedures carried out on blood In most instances the analysis of both blood and urine is more useful than that of either alone The results of determinations *of lead in samples of blood or urine* should be ignored utterly by the clinician unless he has sound reason for trusting their reliability The procedures of sampling *and analysis require special* knowledge and experience for their proper performance and grossly incorrect and utterly misleading results are obtained regularly unless special facilities are available

The threshold value in the blood which is indicative of a clinically significant degree of absorption of inorganic lead is fairly sharply defined at 80 micrograms per 100 gm of whole blood The corresponding value in the urine is somewhat less sharply defined at about 200 micrograms per liter It is unwise to depend upon the results obtained by the analysis of samples of urine of small volume or of one sample of large volume (1 to 2 liters or more) unless it is accompanied and confirmed by analysis of the blood *The demonstration of the presence of high levels of lead concentration in the urine and blood of the patient or in the tissues at necropsy is not in itself evidence of lead*

intoxication These findings must be accompanied by evidence of illness that is characteristic of or consistent with the disease

Prevention It is sufficient for the purposes of this presentation to point out that the medical and engineering techniques of industrial hygiene are adequate to prevent occupational lead poisoning when rigorously employed Despite this fact many cases of industrial lead poisoning are seen by physicians in private practice and it is essential that the latter should take steps to prevent the recurrence of such illness among their patients They should also be alert to preventive measures in the community and especially in the household since they more than any other persons have the opportunity to recognize the nonoccupational hazards in the environment of the families under their care The physician should find out whether or not the industrial conditions which led to his patient s bout of intoxication have been corrected if they have not he should stimulate the necessary corrective action He should not permit his patient to incur further exposure without at least assuring himself that the "body burden" of lead of his patient as revealed analytically has reached a reasonable approximation of a normal level The causes of nonoccupational lead poisoning in the adult or infant should be established if possible and corrective measures should be advised

Treatment The first step in the treatment of lead poisoning is to terminate exposure and absorption Once exposure has been obviated absorption may be reduced and ended by the judicious use of saline cathartics in patients who are obstipated and who may have significant amounts of lead in their alimentary tracts

The therapy of lead poisoning is designed to combat certain clinical manifestations of the disease which in themselves may result in death or serious sequelae to relieve distressing symptoms and to promote the elimination of lead from the body There is no antidote as such for the effects induced by lead when it is present in the body in toxic concentrations On the other hand the uncomplicated intoxication tends to be self limited and signs of illness subside following the cessation of excessive absorption when the lead content of the body is lowered by normal excretory processes and nutrition can be restored

Lead encephalopathy in early childhood has a mortality of 25 to 30 per cent and produces irreversible brain damage in an appreciable proportion of the survivors The greatest threat to the life and mentality of the child appears to be increased intracranial pressure This has been controlled when other measures have failed by craniectomy and the opening of the dura If such intervention fulfills the hope it has inspired it should be undertaken early in the course of the serious case in order to prevent serious brain damage

In tetraethyl lead poisoning with its potentially high mortality death appears to result from exhaustion since apparently successful therapy has combined prolonged and intensive sedation by the use of barbiturates with general nutritive and supportive therapy

The avoidance of permanent paralysis and contracture as sequels of severe extensor weakness or paralysis of the extremities appears to depend in large part upon early recognition of the partial disability prompt and sufficiently prolonged discontinuance of occupational absorption of lead and appropriate physiotherapy including splinting when indicated The administration of large doses of vitamin B_1 has been regarded by some as advantageous

Colic the most distressing symptom in the usual adult patient is best relieved by the slow intravenous injection of 10 ml of a 20 per cent solution of calcium gluconate A similar amount may be given intramuscularly to prolong the effect Other drugs which relax smooth muscle may be used effectively for the relief of lead colic There is a fairly general belief however that calcium salts give relief more completely and more promptly

The anemia of lead poisoning can be treated in the same way as any other secondary anemia Only in those situations in which nutrition has been and continues to be a serious problem does it seem to be relatively intractable

Expediting the elimination of lead from the body is of great importance The simplest and best way of accomplishing this objective short of the use of agents like dimercaprol (BAL) or edathamil disodium calcium (disodium calcium versenate) is to increase the output of water The rate of urinary output of lead can be increased by almost one half by merely doubling the fluid intake this does not produce significant electrolyte loss In itself the forcing of fluids is not recommended as an adequate method of therapy but it constitutes a valuable adjunct to treatment No other known therapeutic procedure can achieve comparable increase in the elimination of

lead other than the two agents indicated above Therapeutically induced shifts in the acid base equilibrium of the body as well as gross changes in the calcium metabolism fail to influence significantly the retention of lead within or its loss from the body

The administration of BAL promotes a brief and highly dramatic change in the distribution of lead in the soft tissues of the body including the blood which in essence is characterized by a prompt release of lead from the erythrocytes into both the soft tissues and the urine Within minutes after the administration of this agent and for some hours the urinary excretion of lead is greatly augmented After eight to twelve hours however the concentrations of lead in the blood and urine will have returned approximately to the levels found prior to treatment the end result being that a few milligrams of lead an insignificant fraction of that which has been added to the body stores have been lost from the tissues mostly from the blood Some degree of risk is associated with this procedure at least theoretically in that the lead-dithiopropanol complex is not free of toxicity Since this therapy neither relieves symptoms nor promotes lead excretion effectively this form of therapy has nothing to recommend it

The intravenous administration of edathamil disodium-calcium has not proved to be a dependable means of relieving the symptoms of lead poisoning of the usual type *e g* colic nor of saving seriously threatened lives This form of therapy does promote effectively the loss of lead from the body and serves to reduce the duration of the period in which symptoms of intoxication may recur There is also some suggestive evidence that it shortens the period of illness and disability An acceptable therapeutic regimen is that of administering this drug in dosages up to 60 mg per kg of body weight per day by intravenous drip in saline or glucose solution (There appears to be no contraindication to the administration of this same dose in 2 subcutaneous injections per day) This is repeated daily for five days and after an interval of seven to ten days after the fifth day of treatment the level of lead concentration in the blood is determined If as will often be the case the concentration of lead is within the dangerous range (0 08 mg or more per 100 gm) the five day course of treatment is repeated These interrupted courses of therapy continue until the concentration of lead in the blood is within the normal range (not in excess of 0 06 mg per 100 gm) By the time the lead in the blood has reached this level the symptoms of the adult patient will have subsided and he will be on the road to recovery The problem of the child recovering from encephalopathy as well as that of the adult who anticipates his return to work are still ahead however in that both may have in their skeletons after the removal of most of the lead from their soft tissues quantities of lead which while equilibrium between the skeleton and the soft tissues is being restored may raise the lead content of the latter to dangerous levels At such a time the concentration of lead in the blood will not have returned to its initial high level but it may be considerably in excess of 0 08 mg per 100 gm For this reason in the further management of the case the concentration of lead in the blood should be determined at intervals of a month or six weeks after the successful response to the first several courses of therapy and the therapy should be resumed as often as the blood level returns to the dangerous range

A less precise therapeutic regimen is necessary when the timing of the steps in this procedure cannot be dictated by the results obtained from the analytical laboratory and a simpler regimen can be employed successfully in the ordinary case of industrial lead intoxication Thus three or four courses of treatment separated by intervals of a week can be given to any patient and when it is known that the patient s exposure to lead was severe or prolonged further courses can be given It is doubtful however that the best and most favorable therapy can be provided especially for a dangerously poisoned child without precise analytical information from time to time as to the extent to which the therapy has accomplished its purpose

In view of the greatly diminished effectiveness of edathamil disodium calcium when administered by mouth and because of the lack of effective control of the therapy itself or of the beneficial or potentially harmful effects induced by its use there seems to be no good reason for administering it orally

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Methemoglobinemia and Sulfhemoglobinemia

(Enterogenous Cyanosis)

Definition Methemoglobinemia exists when a greater than normal concentration of methemoglobin is present in the circulating red blood cells Sulfhemoglobin is not normally present in the circulation The two conditions are frequently coexistent and when clinically apparent are characterized by a cyanosis which differs from that produced by excessive amounts of reduced hemoglobin

Biochemistry In hemoglobin the iron atom is in the ferrous state and is bound by coordinate bonds to the four nitrogen atoms of the pyrrole rings There are two free coordinate bonds which permit reversible oxygenation to form oxyhemoglobin Methemoglobin is formed when the iron is oxidized to the ferric state In this form it cannot be oxygenated and is therefore useless for oxygen transport The oxidation is quite reversible and methemoglobin is readily reduced to hemoglobin by appropriate reducing systems

The precise chemical structure of sulfhemoglobin has not been determined It may be produced by the action of hydrogen sulfide on oxyhemoglobin Sulfhemoglobin cannot be oxygenated nor can it be reconverted to hemoglobin

An aqueous solution of hemoglobin in contact with oxygen is almost wholly oxidized to methemoglobin In oxygenated plasma however dissolved hemoglobin reaches an equilibrium in which only slightly more than half is in the form of methemoglobin while in the normal erythrocyte an equilibrium is maintained in which less than 1 per cent is in the form of methemoglobin

The equilibrium in plasma depends on the presence of normally occurring reducing substances that of the red cell requires the activity of a rather specific enzyme system Lysis of the erythrocyte inactivates this system which uses glucose and lactate There is evidence which suggests that its function depends on an adequate and continuing supply of reduced DPN

Methemoglobinemia occurs whenever there is dysfunction of this enzyme system or when oxidants in the circulation oxidize hemoglobin at a rate which exceeds the reducing capacity of the system

The determinants of sulfhemoglobin concentration are not well understood In clinically encountered concentrations its presence does not significantly alter the life span of the red cell Since it cannot be reconverted to hemoglobin it leaves the circulation only when the red cell containing it is destroyed When the factors which caused sulfhemoglobin formation are removed its concentration diminishes by slightly less than 1 per cent of its initial value per day

Pathological Physiology Acute or secondary methemoglobinemia has two detrimental effects on the organism First that portion of hemoglobin which is oxidized to methemoglobin is no longer available for oxygen transport and the condition is analogous to an anemia of comparable degree Second Darling and Roughton demonstrated that the presence of methemoglobin in the circulation altered the dissociation curve of the remaining oxyhemoglobin in such a way that tissue oxygen tensions must fall to lower than normal values before the remaining oxyhemoglobin yields its oxygen This is analogous to but less marked than the shift in oxyhemoglobin dissociation curve caused by carboxyhemoglobin

Methemoglobinemia of less than 40 per cent produces little respiratory or cardiovascular change at rest but concentrations of 10 to 20 per cent are accompanied by significant elevations of blood lactate in men who are performing moderately heavy work

Similar handicaps are thought to be imposed by sulfhemoglobinemia but these have not been studied in detail

Etiology Primary or congenital methemoglobinemia (*q v*) is an inborn error of metabolism caused by failure of function of the intracellular reducing enzyme system

Secondary or acute methemoglobinemia is produced by a group of compounds the nature and mode of action of which have

been extensively reviewed by Bodansky These compounds include direct oxidants which can be observed to have a powerful *in vitro* action and a large group of aromatic nitro and amino compounds with little or no direct oxidant action *in vitro* but very powerful methemoglobin formation *in vivo* In spite of intensive study the nature of the intermediate compound by which this group produces methemoglobinemia has not yet been firmly established

The direct oxidants include nitrites chlorates and quinones Nitrates particularly in infants may be reduced to nitrites by bowel action severe methemoglobinemia in infants has followed the ingestion of nitrate contaminated well water and the use of bismuth subnitrate for diarrhea

Three important groups among the indirect oxidants merit discussion

1 *Aniline and Its Derivatives* Diapers freshly stamped with aniline marking ink have caused dangerous and even fatal methemoglobinemia in infants Similar poisonings have been caused by percutaneous absorption from freshly dyed shoes and blankets Aniline derivatives are also responsible for the methemoglobinemia which may be caused by the ingestion of colored wax crayons

2 *Earlier Sulfonamide Derivatives* High blood concentrations of sulfanilamide Prontosil sulfathiazole and sulfapyridine are almost uniformly accompanied by some degree of methemoglobinemia This has been very rare and mild with sulfadiazine and sulfamerazine

3 *Acetanilid and Phenacetin (Acetophenetidin)* Analgesics containing these two compounds may be obtained without prescription and are consumed in enormous quantities they are among the most common causes of methemoglobinemia and sulfhemoglobinemia

Sulfhemoglobinemia may be produced *in vivo* by most of the compounds which cause methemoglobinemia and the two conditions frequently coexist

Enterogenous Cyanosis Under this heading a small and clinically rather ill defined group of cases caused great interest in the first quarter of this century They were characterized by sulfhemoglobinemia and/or methemoglobinemia Bowel dysfunction was found in the great majority and headache was a frequent symptom The disorder was thought to be caused by the absorption of an enterogenous oxidant Shortly after 1925 when it was demonstrated that phenacetin could produce sulfhemoglobinemia as well as methemoglobinemia this entity practically disappeared from the literature

Symptoms and Signs In mild cases cyanosis is often the main symptom as well as the cardinal sign In more severe instances this is accompanied by the syndrome of acute hypoxemia with exertional dyspnea headache dizziness and blurring of mental functions In extreme instances this syndrome may progress to stupor or even coma

Diagnosis Whenever cyanosis exists without concomitant evidence of cardiovascular or respiratory dysfunction the presence of methemoglobinemia and/or sulfhemoglobinemia should be suspected If venous blood retains its brownish hue when it is shaken vigorously with air for fifteen minutes suspicion is confirmed under these conditions reduced hemoglobin is almost completely oxygenated to scarlet oxyhemoglobin Examination of a 1 100 aqueous dilution of blood with a hand spectroscope finally establishes the diagnosis Methemoglobin shows a well defined absorption band at 630 $m\mu$ which disappears almost immediately after the addition of a few drops of 5 per cent KCN solution sulfhemoglobin s absorption band at 618 $m\mu$ is unaffected by the addition of KCN Quantitative studies require more complex spectrophotometric and gasometric techniques

Treatment Mild cases require no treatment other than the withdrawal of the causative chemical Concentrations of sulfhemoglobinemia sufficient to endanger life do not seem to occur clinically and there are no known measures which will convert sulfhemoglobin to hemoglobin The reducing enzyme system of the erythrocytes will rapidly reconvert methemoglobin to hemoglobin when the disturbing oxidant disappears from the circulation

If the degree of methemoglobinemia is of sufficient degree to cause significant hypoxia an intravenous solution of 1 per cent aqueous methylene blue in dosage of 1 0 to 2 0 mg per kg of body weight should be administered If injected over a period of several minutes this dosage causes no undesirable side effects in man and very rapidly reconverts methemoglobin to hemoglobin If methemoglobinemia recurs as a result of the persistent action of some agent such as nitrobenzene the administration of methylene blue may be repeated at hourly intervals

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Chronic Bromide Poisoning

(*Bromism*)

Definition Chronic bromide poisoning occurs when the bromide ion is ingested in amounts or under circumstances which cause its concentration in body fluids to rise to levels at which its depressant action produces toxic effects on the central nervous system This level varies widely in different individuals but may be as low as 50 mg per 100 ml

Etiology The bromide ion is as readily absorbed as the chloride ion and is distributed through the same fluid compartments Under normal conditions renal homeostatic mechanisms maintain the *total plasma halide concentration* relatively constant at approximately 100 mEq per liter The renal tubule normally reabsorbs a slightly higher percentage of filtered bromide than chloride ion Whenever the bromide ion constitutes a significant proportion of ingested halide the bromide concentration in body fluids rises until an equilibrium is reached at which renal excretion equals ingestion

Incidence Wuth s classic article in 1927 recorded that 21 per cent of the patients admitted to the psychiatric division of the Johns Hopkins Hospital over a period of six months had bromides in their blood and signs of intoxication In 7 7 per cent of a series of patients admitted to a state psychopathic hospital excessive blood bromide concentrations were found unsuspected bromide intoxication was the sole reason for the admission of almost 2 per cent In spite of continued published warnings the incidence of bromism is still appallingly high

Among the several reasons for this sad state of affairs are (1) The symptoms of the underlying disturbance for which bromides are taken and those of bromism itself are often very similar since bromide may temporarily alleviate the very symptoms it produces increasingly large amounts may be administered to a person already suffering from bromism (2) Many proprietary "nerve tonics and analgesics contain significant quantities of bromides and may be obtained in unlimited quantities without prescription (3) Even physicians may overlook the fact that the toxicity as well as the efficacy of a given dosage of bromide ion can be estimated only when the patient s total halide intake is known a dosage which may be totally ineffective in a person with a high salt intake may rapidly produce severe poisoning in a patient on a cardiac regimen with markedly limited chloride ingestion Finally complications such as arteriosclerosis alcoholism and systemic disease may increase a patient s susceptibility to bromide intoxication

Symptoms The symptoms of bromism vary greatly from patient to patient not only in their pattern but in their relationship to the blood bromide level Among the chief symptoms in order of frequency are headache irritability emotional instability weakness lethargy slurred and irrelevant speech disorientation hallucinations and loss of memory The Council on Pharmacy and Chemistry of the A M A noted that any organic reaction type may be simulated

Bromide rash is found in less than 25 per cent of cases of bromism

Diagnosis Although a high index of suspicion is a prerequisite the symptoms and signs of bromism are so protean and so subtle and often so similar to those of the disorder for which bromide is administered that it is only through the determination of the concentration of bromide ion in the blood that suspicion can be substantiated Wuth s gold chloride method is readily performed and is accurate enough for clinical purposes The correlation between symptomatology and blood bromide concentrations is only rough but concentrations of 75 mg per 100 ml and more are suggestive and concentrations more than twice this are definitely toxic

Treatment Bromide ingestion is stopped and renal elimination of bromide ion from the body is speeded by means of a high fluid and chloride intake supplemented by mercurial diuretics which significantly increase bromide clearance If the patient s

cardiac status permits fluid intake is increased to about 4 liters a day Chloride intake is augmented by the administration of 6 gm each of enteric coated ammonium and sodium chloride

Dialysis by means of the artificial kidney will very rapidly remove bromide ion from the body but such heroic therapy is infrequently indicated

The rate of bromide ion excretion by the kidney falls as the blood bromide concentration diminishes so that many months may be required completely to rid the body of bromide Symptoms and signs of bromide intoxication may outlast by days or weeks the return of blood bromide concentrations to accepted therapeutic values

The restlessness exhibited by most patients with severe poisoning has been difficult to control with conventional sedatives chlorpromazine has been reported to be of value under these circumstances

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Salicylate Poisoning

Definition The administration of sufficiently large dosages of salicylates produces a group of symptoms known as salicylism characterized by headache dizziness tinnitus diminution in hearing mental confusion sweating nausea vomiting and upper abdominal discomfort occasionally with gastrointestinal hemorrhage

Higher plasma salicylate levels cause stimulation often followed by depression of the central nervous system Concurrently significant changes in the acid base and electrolyte structure of the body fluids are produced These disturbances are known as "salicylate poisoning

Incidence More than 9 000 000 pounds of aspirin (acetylsalicylic acid) alone are consumed annually in the United States Although the relative incidence of poisoning among the millions of users is low the absolute figure represents a substantial and needless loss of life In 1952 there were 113 reported deaths from salicylate poisoning 86 of these occurred in children under five years of age

Morbid Anatomy Petechial hemorrhages in the central nervous system and in various viscera are a prominent feature Recent studies of the brains of patients who died of salicylate poisoning demonstrate direct nerve cell damage and the lesions of a toxic encephalopathy

Pathological Physiology and Chemistry Salicylates specifically increase the sensitivity of the respiratory center to the CO hydrogen ion stimulus Blood salicylate concentrations ranging from 12 to 16 mg per 100 ml increase the sensitivity of the center from 84 to 307 per cent This is accompanied by a striking increase in minute respiratory volume Individual sensitivity to a given concentration of salicylates varies widely although 35 mg per 100 ml has been cited as the toxic level in children unequivocal instances of toxicity have been observed in acutely ill children with blood levels as low as 9 mg and less per 100 ml

The increased respiratory minute volume leads to a fall in arterial CO tension and CO_2 content and a rise in pH The rise may be sufficient to produce frank tetany Renal excretion of fixed cations lessens the pH increase In the milder instances of salicylate poisoning usually seen in older children and adults this picture of respiratory alkalosis with slight reduction in buffer base predominates In more severe cases in adults and older children and in most cases of children under six years old this phase is followed by a significant fall in buffer base and the appearance of a true metabolic acidosis

The acidosis cannot be accounted for by the actual quantity of salicylate present and the relatively small renal excretion of fixed cation in respiratory alkalosis It is hypothesized that the salicylate in these cases interferes with oxidative enzyme systems

Large doses of salicylates also cause prothrombinopenia

Symptoms and Signs In adults the symptoms of salicylism usually precede salicylate poisoning In children these are rarely noted and hyperpnea and vomiting are the striking manifestations Fever is a prominent feature of the most severe degree of poisoning and sweating often adds to the

dehydration In instances of therapeutic overdosage they are superimposed on the syndrome of the underlying disease

Convulsions delirium and coma are observed not infrequently in grave poisonings

Diagnosis Unexplained hyperpnea and vomiting in a child should raise the possibility of salicylate poisoning Since hyperglycemia may occur in salicylate poisoning the differentiation from diabetic acidosis must be kept in mind The presence of salicylates in urine may be established by adding ferric chloride and observing a purple ring which does not disappear with boiling Determination of the blood salicylate concentration will confirm the diagnosis

Prognosis Prognosis must be guarded fatalities have occurred after electrolyte disturbances have been restored to normal

Treatment In instances of accidental poisoning gastric lavage with tap water should be performed at once methyl salicylate in particular may remain in the stomach for many hours

Unless facilities are available for the accurate determination of arterial or capillary blood pH and CO content intravenous therapy should be restricted to the administration of physiological saline solution to combat dehydration and of glucose for ketosis If these parameters can be precisely measured cautious correction of the pH and electrolyte disturbances should be attempted In contrast to the situation in methanol poisoning one should err on the side of under rather than overtreatment

Prophylactic administration of 50 to 75 mg of menadione sodium bisulfite and of up to 0 5 gm of ascorbic acid in adults is worthwhile Vitamin K_1 oxide should be given for active bleeding

Controlled intermittent positive pressure respiration after curarization using equal mixtures of nitrous oxide and oxygen in a closed system has been favorably reported If the necessary trained team is available and the gravity of the poisoning warrants it salicylate concentrations can be rapidly reduced and normal electrolyte structure restored by dialysis with the artificial kidney

Since the central nervous stimulation caused by salicylates is frequently followed by depression sedation of any sort must be administered with great caution Calcium salts and CO inhalation have little if any value

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Methyl Alcohol Poisoning

Methyl alcohol (wood alcohol methanol) is widely used as an industrial solvent but its current medical importance stems from its employment as an adulterant of or substitute for ethyl alcohol in beverages

Incidence Outbreaks of methanol poisoning usually occur when access to beverages containing ethyl alcohol is restricted by regulation or when economic conditions and a high tax on beverage alcohol encourage its use as an adulterant Lack of appreciation of its terrible toxic properties is in part the responsibility of the medical profession which was long confused by its apparent lack of toxicity in several species of commonly used experimental animals A single batch of illicit whiskey produced 323 cases of poisoning and killed forty one people

Morbid Anatomy Meningeal petechial hemorrhages and submucosal subepicardial and subpleural hemorrhages are usually seen Cerebral edema and necrosis of the retinal neurons are consistent autopsy findings but the optic nerves and tracts are usually spared Severe pancreatic necrosis secondary to acute hemorrhagic pancreatitis is frequent in fatal cases

Pathological Physiology and Chemistry Methanol like ethanol produces an irregularly descending depression of the central nervous system In equal doses this intoxicant action of methanol is much less than that of ethanol The noxious action of methyl alcohol results from the severe acidosis produced by it in primates and a highly specific reaction of its metabolites on the neurons of the retina As little as 6 ml has caused death and blindness has been reported after the ingestion of only 4 ml On the other hand survival after drinking as much as 540 ml has been observed

Gastrointestinal absorption of methanol is prompt but a latent period between in

gestion and the appearance of toxic symptoms is usually observed this latent period is usually about twenty four hours although it may range from less than one to more than forty hours

Methanol is oxidized in the body to formic acid formaldehyde is a probable step in this oxidation The severe acidosis observed in many patients (four patients in the Atlanta outbreak showed a carbon dioxide combining power of *zero* as determined by the Van Slyke method) cannot be accounted for by the quantity of formate formed It is postulated that methanol and/or its metabolites inhibit some oxidative enzyme systems and permit the accumulation of lactic and unidentified organic acids

In excised liver slices and in experimental animals methanol is oxidized only one seventh as rapidly as ethanol it may persist in the body for as long as a week after ingestion The presence of ethyl alcohol significantly retards the oxidation of methanol

Symptoms and Signs The symptoms of methyl alcohol poisoning are usually complicated by those of varying degrees of ethanol intoxication since both alcohols are usually ingested simultaneously Visual disturbances and abdominal pain are among the most characteristic and headache is common Dyspnea is an infrequent complaint

Dilated nonreactive pupils hyperemia of the optic disks with varying degrees of retinal edema and rigidity of the abdominal muscles are striking physical signs The skin is often cool and clammy Kussmaul breathing is not prominent

Diagnosis Methyl alcohol poisoning should be considered in any patient complaining of abdominal pain and visual disturbance Suspicion should be heightened by a history of a recent drinking bout and hyperemia of the optic disks and acidosis in association with these makes the performance of a specific test for methanol in the blood worthwhile

Prognosis Since death from respiratory failure may occur in spite of correction of the acidosis prognosis must be guarded The likelihood of permanent visual impairment is almost impossible to assess at the outset

Treatment *Whenever a case of methanol* poisoning is diagnosed efforts should be made to bring under medical observation all persons who ingested the same beverages as did the patient

The cornerstone of treatment is the correction of the acidosis Enormous amounts of alkali may be required as much as 420 gm of sodium bicarbonate have been administered in twenty-eight hours with benefit Serum carbon dioxide content or capacity should be determined at the start of treatment and the course of therapy followed with serial determinations Since vomiting is often a problem alkalinization is usually best accomplished by the intravenous administration of a 3 to 5 per cent solution of sodium bicarbonate in 5 per cent dextrose and water The slow oxidation of methanol may lead to recurrence of acidosis after initial correction and may require further therapy After therapy is under way hypokalemia should be watched for and treated if necessary

Current evidence suggests that the toxic effects of methanol may be lessened and even prevented by the concurrent administration of ethyl alcohol a maintenance level of 0 1 per cent ethanol is suggested In a person whose blood contains none this level may be promptly achieved by administering 60 ml of ethanol and it may be kept at this level by giving 9 ml per hour

The eyes should be protected from light Supportive measures such as oxygen for hypoxia and short acting intravenous barbiturates for convulsions are used as indicated

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Radiation Injury

Definition The term radiation injury" describes a number of clinical syndromes which have exposure to ionizing radiation as a common etiology The term radiation sickness has generally been used to designate the nausea and loss of appetite which follow exposure to penetrating radiations

used for therapeutic purposes Radiation injury in a less restrictive sense is reserved to indicate those clinical and subclinical manifestations which result from toxic local or general exposure to penetrating radiations originating from an external source or from the presence of radio elements within the body itself For practical purposes the agents capable of producing injury to the body are x rays gamma rays fast and slow neutrons beta and alpha particles Radiation which arises from sources outside the body is conventionally referred to as external radiation while radiation arising from radio-elements within the body is referred to as internal radiation

Etiology Beta particles are energetic electrons which travel several millimeters in tissues ordinary alpha particles are helium nuclei which travel a maximum of about 40 microns in tissue whereas energetic x rays gamma rays or fast neutrons are many times more penetrating than either X rays and gamma rays expend their energy and produce biological effects in cells and tissues by the acceleration of electrons fast neutrons by acceleration of protons (hydrogen nuclei) and slow neutrons by the release of gamma rays or fast atomic nuclei when they are captured by the atomic nuclei of the chemical elements present in the tissue Thus the significant ources of external radiation include all those mentioned except alpha particles Internal radiation involves alpha and beta particles and gamma rays

The clinical manifestations of exposure to radiation vary because the injury sustained depends on the type and energy of the radiation the area of the body exposed and the dose and the length of time over which a given dose is sustained The biological effects of penetrating ionizing radiation delivered to the whole body within a few milliseconds or minutes will differ remarkably from the effects resulting if this same amount of radiation is sustained over a period of weeks months or years The degree of selective localization of radio elements within the body and the half life of the isotope are additional factors to be taken into consideration

Radiation exposure until 1934 was largely confined to professional and technical personnel involved in the preparation of radium and its by products to persons employed in the manufacture of x ray tubes and equipment or engaged in the diagnostic and therapeutic use of x rays and gamma rays and to a lesser extent to persons using these radiations as tools of physical research The invention of the cyclotron by Lawrence in 1934 brought the added hazard of the fast neutron and gamma rays and artificial radio-elements In 1942 the first chain reacting uranium pile was placed in operation by Enrico Fermi adding as a consequence a radiation hazard several thousand times greater than that which had existed theretofore Thus the uranium pile the processing of the many radio-elements produced in the fission reaction and the increased medical and research uses of radiation and radio elements and the eventuality of atomic warfare make the prevention diagnosis and treatment of acute and incipient radiation injury a public health problem of growing national importance

The entry of radioactive elements into the body may occur as a result of ingestion (deliberate or accidental) inhalation introduction through penetrating wounds absorption through the skin or deliberate intravenous administration as in the use of these materials for therapeutic purposes

Units of Measurement and Permissible Exposure In 1931 a committee established by the National Bureau of Standards set 0 1 roentgen (r) per day of x rays or gamma rays as the permissible dose to which the human body could be exposed indefinitely without the production of harmful effects The r is the unit of exposure dose and is that amount of radiation which will result in the absorption of 83 ergs per gm when wet tissue is exposed to it

Later in 1951 the maximal permissible level of exposure was lowered to 0 3 rem per week by the National Committee on Radiation Protection The rem unit is that amount of radiation of any type which has the same biological effectiveness as 1 rad of 200 kv x rays The rad is a unit of measurement that is rapidly becoming accepted as the most accurate and universal expression of dose It is a unit which expresses the absorbed dose and is 100 ergs per gm of the absorbing medium

It should be emphasized that the maximum permissible level of radiation for human beings is subject to many qualifying considerations *e g* age condition of health general or selected population and so forth A comprehensive discussion of the subject may be found in Handbook 59 Permissible Dose from External Sources of Ionizing Radiation National Bureau of Standards 1954

Experimental Radiation Injury Experiments on animals have been performed to give baseline information and to supplement the very limited data that are available *on the effects of ionizing radiations* in human beings The reader is referred to papers by Prosser Lorenz Friedman Dunlap and Jacobson since only a brief summary of these studies is presented here

Single Exposure (Whole Body) to Dosages in the Midlethal Range The dosages of x radiation required to kill half of irradiated groups of animals (within thirty days) of the species commonly used in laboratories are

Guinea pig	250 roentgens
Dog	325 roentgens
Goat	350 roentgens
Mouse	550 roentgens
Rat	650 roentgens
Rabbit	800 roentgens

In all these species death usually occurs between the sixth and the fourteenth days The chief pathological findings are confined largely to the hematopoietic system the gastrointestinal tract and the gonads Doses below the midlethal point produce progressively less damage in these species Single doses below 25 roentgens produce neither hematological nor histopathological evidence of effect

Repeated Exposure (Whole Body) to Relatively Low Dosages in the Permissible Range Experiments on mice guinea pigs and rabbits indicate that a dosage of 0 1 *roentgen per day (radium gamma rays)* is tolerated throughout the normal life span of the animal (more than three years) without the appearance of recognizable evidence of damage except for an increased incidence of ovarian tumors in female mice With dosages of 1 2 4 or 8 roentgens per day the hematopoietic depression shortening of the life span and the incidence of sterility and of benign and malignant tumors becomes increasingly more significant

Morbid Anatomy The pathological changes associated with whole body exposure to lethal or semilethal doses of penetrating radiations (400 to 600 roentgens) as described by Warren are essentially limited to the findings of an aplastic marrow depletion of lymphatic tissue destruction and atrophy of gonadal tissue edema mucosal sloughing and hemorrhage in the gastrointestinal tract multiple pyogenic abscesses or other infection hemorrhages in the skin subcutaneous tissue muscle and viscera and an increase in tissue mast cells Erythema edema loss of skin surface with delayed healing and epilation are common after exposure to doses of about 600 roentgens or more Doses below the lethal range produce correspondingly less pathological change

Acute or chronic exposure to whole or partial body radiation below the lethal but above the permissible range may produce no demonstrable pathological effects or the effects may be confined to degenerative changes in the hematopoietic system gonads skin and eyes and to the induction of neoplasms

The pathological changes associated with radioactive elements such as radium strontium and plutonium which are deposited largely in bone are a hyperplastic immature or aplastic type of marrow rarefaction of bone fracture and incomplete healing irregularities of the epiphysis and growth arrest As described by Martland sarcomas of bone are complications of these long lived bone seekers

Pathological Physiology and Chemistry Absorption of radiation in cells and fluids of the body is attended by release of energy This release of energy is considered by many authorities to consist of transient ionization of water molecules followed by the formation of hydrogen peroxide and chemical radicals which in turn inhibit or denature the sensitive enzymes or enzyme systems There is a great difference in the radiosensitivity of cell types within the body The radiosensitivity of the same cell type differs from person to person and from species to species Rapidly proliferating cells such as lymphocytes and spermatogonia are more radiosensitive than the cells of the brain or the kidney Cells in mitosis especially in prophase are more susceptible to radiation injury than cells in the resting phase It is also apparent that a latent period varying from minutes to years may be interposed between the initial effect of irradiation on cells and their death or functional derangement

In acute lethal or midlethal radiation injury regeneration and repair proceed too slowly to overcome the overwhelming pathological alteration induced by the widespread death of cells In chronic radiation exposure regeneration and repair may so closely parallel injury that pathological alteration does not become manifest for long periods of time if at all

No single organ system or tissue appears to be universally critical in producing death after lethal or midlethal whole body exposure to single doses of external radiation Death appears to occur usually as a result

of a combination of pathological processes which include plasma and electrolyte loss destruction of hematopoietic tissue infection hemorrhage and nonspecific toxemia

The functional effects of acute or chronic external exposure such as temporary or permanent sterility and amenorrhea can usually be correlated directly with pathological changes in the ovary or testes On the other hand the altered capillary physiology the role of histamine release the loss of adrenal lipid the increased incidence of neoplasia and accelerated aging process are as yet poorly understood from the standpoint of the mechanism of the acute or chronic radiation injury syndrome

Symptoms and Signs Injury from overwhelming doses to the whole body is followed within minutes to hours by severe nausea vomiting and diarrhea erythema and edema of the skin severe prostration circulatory collapse coma and death within forty-eight hours

Lethal or near lethal doses (400 to 600 roentgens) produce severe weakness malaise and prostration nausea and vomiting and diarrhea within a few hours after exposure Fever appears within the first twenty four hours Infections such as painful ulcerations in the throat or about the teeth skin abscesses or evidence of other local or more general infection appear after two to four days Bleeding from the gums and bloody diarrhea usually appear at the end of the first week after exposure and may increase in extent and severity through the third week or more unless recovery or death occurs Disorientation may appear early and progress to coma If patients survive infection hemorrhage and shock resulting from plasma and electrolyte imbalance in the first three to four weeks anemia may be sufficiently severe as a result of hemorrhage and failure of marrow recovery to produce death Temporary or permanent sterility amenorrhea and an increased incidence of acute and chronic leukemia are observed in survivors

Whole body exposure to single doses of 200 to 400 roentgens of penetrating radiation can be expected to produce marked weakness malaise nausea vomiting and diarrhea Individual susceptibility will dictate the outcome of persons in the group in the absence of supportive treatment All will have leukopenia and thrombocytopenia but the seriousness of infection anemia hemorrhage and electrolyte imbalance will vary from mild to severe Death can be expected to occur in less than 50 per cent of this group from circulatory collapse infection hemorrhage or combinations thereof Temporary sterility and epilation will occur in an unpredictable number of the persons thus exposed

Single doses of 100 to 200 roentgens can be expected to produce nausea vomiting anorexia malaise fever and diarrhea These symptoms would appear early but would be transient Leukopenia and thrombocytopenia would occur but variability in the severity should be expected Hemorrhagic manifestations would be moderate or absent an anemia would be unlikely Recovery could be expected in all persons so exposed

Single doses of 50 to 100 roentgens produce no symptoms or only a mild nausea and malaise Reduction in leukocyte and platelet values of the peripheral blood may occur in an occasional person but will be transient No symptoms or signs occur from whole body exposure to 25 roentgens or less

Injury from chronic exposure to radiation of external origin produces local or general symptoms and signs depending on whether whole or partial body exposure was sustained Delayed healing of abrasions or the development of painful benign or malignant ulceration in the friable atrophic skin of the hands may be distressing Weakness and fatigue are associated with the onset of a leukemia or the presence of an anemia and may also occur in circumstances in which only a leukopenia is demonstrable Premature menopause with its attending symptoms in the female and sterility in the male with aspermia or morphologically abnormal sperm may occur The development of lens opacities is attended with a gradual loss of vision

The clinical picture produced by lethal amounts of radioactive elements such as radiophosphorus (P^{3}) or radiostrontium (Sr^{89}) is similar in most respects to that observed after lethal doses of whole body radiation from an external source except that the onset of symptoms is delayed The symptoms preceding death are chiefly due to severe anemia leukopenia and thrombocytopenia with widespread hemorrhage or infection or both since these radioactive elements seriously affect the hematopoietic system Lesser amounts of these and other radioisotopes produce signs and symptoms dependent on the degree of localization For example after the administration of radioiodine (I^{131}) in single or divided doses sufficient to produce a remission in hyper

thyroidism hypothyroidism may insidiously supervene as a result of thyroid destruction

Since in therapeutic radiology every effort is made to minimize discomfort to the patient or damage to normal tissue complications are relatively rare Nausea anorexia and malaise are frequently associated with therapeutic radiation involving abdominal viscera diarrhea may supervene in some instances Leukopenia thrombocytopenia and anemia occasionally complicate therapeutic irradiation when the portals involve hematopoietic tissue

Diagnosis The diagnosis of radiation injury after whole body exposure to a single burst of penetrating radiation in or near the lethal range as a result of accidents involving cyclotrons betatrons large gamma ray sources and nuclear reactors will offer no problem the difficulty will be found in establishing the exact or approximate dose received and thus the probable prognosis or in the case of an atomic bomb attempting to distinguish radiation injury from thermal and blast injury With doses below the lethal range but above 100 roentgens the characteristic symptoms of nausea vomiting diarrhea anorexia and malaise are likely to appear within hours of the exposure the leukopenia and thrombocytopenia follow within a week and anemia even later Temporary complete or partial epilation temporary sterility in both males and females and temporary amenorrhea in women should always be looked for after exposures in this range The diagnosis of radiation injury after accidental or therapeutic exposure of a part of the body to single or divided doses of penetrating external radiation may rest on the history since the local findings the symptoms and hematological picture will depend to a large extent on the size of the area irradiated and the total dose sustained

The diagnosis of radiation injury from chronic exposure to external radiation above the permissible range is based on the history of exposure plus such findings as dermatitis atrophy or distortion of the epidermal ridges of the fingers hyperkeratosis epilation indolent skin ulcers neoplasia sterility amenorrhea lens opacities and hematological abnormalities

Even in the presence of suggestive clinical or laboratory evidence of radiation injury from internal emitters such as radium and plutonium the diagnosis must be confirmed on the basis of the demonstration of evidence of actual deposition within the body This may be done by survey of the body with a modified Geiger counter or isolation and identification of the radio element in the urine

Treatment In general there is no specific treatment for radiation injury Treatment of radiation injury from single doses in the lethal range consists largely in symptomatic supportive and prophylactic measures Maintenance of fluid and electrolyte balance with physiological saline and other necessary aids combating protein deficiency and vascular collapse by the liberal administration of plasma and whole blood parenteral feeding with glucose and protein digests prevention or management of infection with antibiotics management of blood loss with whole blood transfusion compression bandages for severe surface burns and liberal use of sedation such as morphine for pain and restlessness are the major steps to be taken In the event of an atomic bomb the treatment would be essentially similar except that the flash burns and penetrating wounds would require immediate attention The severe nausea vomiting and diarrhea which attend serious radiation injury respond poorly to any attempt at specific management Persons exposed to doses of whole body radiation below the midlethal range but from which gastrointestinal symptoms infection and hemorrhage of unpredictable seriousness may arise should be managed in accordance with the clinical and laboratory evidence of involvement

The treatment of accidental or deliberate exposure of limited areas of the body to external radiation with injury to vital internal organs or tissues or damage to the skin (erythema) will depend on the area involved and the severity of the pathological process

Treatment of evidence of radiation injury resulting from chronic exposure to penetrating external radiation should begin by removing the person from further exposure or reducing the exposure to permissible or negligible levels Such manifestations as radiation dermatitis atrophy of the skin indolent ulcers carcinoma of the skin leukopenia leukemia and lens opacities will require specific symptomatic supportive treatment or corrective surgery

The treatment of radiation injury following the entrance of massive doses of radio elements into the body is essentially similar to the treatment of massive exposure to penetrating external radiation No effective methods are available which materially hasten the excretion of radio elements fixed in the body The treatment of

the anemia leukopenia thrombocytopenia and hemorrhagic manifestations which follow therapeutic administration of radio phosphorus (P^{32}) radiosodium (Na^{24}) and radiostrontium (Sr^{89}) is largely confined to blood transfusion and the use of antibiotics as indicated if local or general infection occurs

Prophylaxis Prevention of radiation injury involves the maintenance of conditions which reduce the hazard of exposure to external and internal radiation to the permissible dose level or below The techniques involved in working with radiations require special experience and knowledge if chronic overexposure and disastrous accidents are to be avoided Orientation of personnel should precede work with penetrating radiations or radioactive elements Such orientation should embrace (1) understanding of "permissible exposure and basic knowledge of the biological effects and physical properties of radiation (2) understanding of the principles of radiation protection from the various radiations (3) ability to utilize existing instruments for determining a given radiation hazard (4) familiarity with the techniques and procedures basic to work with these physical agents

The supervisor must assume the responsibility for his professional and technical staff and demand and enforce observation of accepted standards of operation One careless person working with radioactive elements can hopelessly contaminate a laboratory and jeopardize the health of his colleagues

Even when the most stringent precautions are enforced to minimize radiation exposure such as education of personnel shielding of radiation sources and effective ventilation the following additional precautions must be observed (1) periodic medical examination which should include a general physical examination with special reference to evidence of atrophic changes in the skin or of dermatitis (2) periodic hematological studies to detect leukopenia thrombocytopenia or anemia (3) daily monitoring of skin and clothing of personnel for contamination with radioactive elements (4) periodic examination of urine sputum feces and exhaled air from personnel to detect actual presence of radio-elements in the body (5) continuous monitoring of personnel during working hours in order to measure dose received (film badge pocket electroscope and so on) (6) periodic monitoring of laboratory facilities or radiation source installation for evidence of radioactive contamination or unsuspected faulty shielding This involves analysis of air samples in certain circumstances

Evidence of actual overexposure of a person (physical measurements) or clinical or laboratory evidence of radiation injury should be followed by immediate removal of the person from all sources of further exposure until the situation can be properly assessed and remedial measures instituted if necessary The decision whether a person once or repeatedly over exposed to radiation with or without evidence of radiation injury may or may not be allowed to continue work with radiation will be difficult to make with certainty

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Hypervitaminosis

History Since vitamins were first used as therapeutic agents there have been sporadic reports of ill effects following their administration Despite the size of the therapeutic dose however the administration of most of the vitamins is not followed by any untoward effects The water soluble vitamins tend to reach a certain concentration in the blood and are then quickly excreted Undoubtedly cases of individual idiosyncrasy may produce unpleasant reactions to these substances *even when taken in* small amounts Such symptoms are not those of hypervitaminosis There is considerable evidence that repeated massive doses of the fat soluble vitamins A and D sometimes produce so-called hypervitaminosis This discussion will be limited to the hypervitaminosis caused by vitamin A *and* by vitamin D

Hypervitaminosis A This term is used for a varied and sometimes bizarre condition arising from the administration of

massive doses of vitamin A Numerous investigators have reported injurious effects following the administration of large doses of vitamin A to rats The coats of the animals become rough and they develop cachexia conjunctivitis and diarrhea striations in the muscle fibers of the heart degeneration of the testes and changes in the liver The excessive administration of vitamin A to young rats and guinea pigs has been associated also with bone fragility and fractures

Although in the human being the administration of up to 300 000 U S P units of vitamin A daily for a number of months has not produced detectable harmful effects some persons have developed sensitivity to cod liver oil It is of interest that the ingestion of polar bear liver results in serious illness which is due to the large amount of vitamin A in polar bear liver at certain times of the year Analysis of polar bear liver shows that it may contain as much as 18 000 I U of vitamin A per gram of wet material Affected persons develop severe headaches and vomiting Although some investigators have not accepted the idea that it is vitamin A which causes toxicity of polar bear liver the author sees no reason to look beyond this Hypervitaminosis A in its chronic form is characterized by anorexia loss of weight sparsity of hair hepatomegaly and tenderness over the long bones which show characteristic roentgenographic changes occurring most frequently in the ulna and tibia The changes consist of a parallel type of periosteal reaction especially in the mid portion of the shafts with swelling of the overlying muscles and soft tissues Calcified rings appear about the epiphyses

Hypervitaminosis D In 1928 and 1929 considerable interest was centered on the effect of administering repeated massive *doses of vitamin D to experimental animals* In a study on normal animals Kreitmair and Moll found that the administration of massive doses of irradiated ergosterol was followed by calcium deposition in some of the tissues In a study of the effect of repeated large doses of irradiated ergosterol to experimental animals with either acute or chronic tuberculosis Spies found extensive deposition of calcium salts within the caseous lesions He also corroborated the findings of other workers who reported *that massive* and repeated dosage of vitamin D was followed by loss of weight cachexia and calcification of many of the tissues In *addition* he observed an even more widespread calcification than had been *reported previously and* a retention of nitrogenous products in the blood which was associated with marked kidney lesions When such toxic manifestations occurred in animals the possible danger of giving repeated large doses in clinical practice was obvious

In human beings *hypercalcemia follows* the repeated administration of large doses of vitamin D Reed believes however that the toxic effects of vitamin D are independent of its action in raising the calcium and inorganic phosphorus concentration in the blood serum Persons treated for a prolonged period of time with massive doses of vitamin may exhibit calcification of the soft tissues

Frequently it is difficult to obtain a history of excessive vitamin D therapy but in all cases of unexplained hypercalcemia the patient should be carefully questioned in regard to vitamin D therapy This is particularly important should an operation for adenoma of the parathyroid gland be considered According to Park early symptoms of overdosage are nausea headache diarrhea loss of appetite frequent micturition nocturia and lassitude Examination of the urine may reveal evidence of overdosage Albright and his collaborators noted that after enormous doses of vitamin D in a child with intractable rickets the urine was loaded with calcium and contained many calcium casts such as have been observed in cases of hyperparathyroidism

Two cases of hypercalcemia with calcification of soft tissues and renal damage have been reported by Danowski Winkler and Peters Bauer and Freyberg have reported a fatal case of vitamin D intoxication in an adult woman who received massive doses of vitamin D for over one year At autopsy white chalky deposits of calcium salt were found in the myocardium kidneys and arteriovascular system In growing children there is a dense deposit of mineral in the zone of provisional calcification in the metaphyses of long bones in addition to metastatic calcium deposits in various organs and in and about joints

Therapy with massive doses of vitamin D for very long periods of time demands careful supervision by the physician Serum calcium should be determined frequently and at the first suggestion of hypercalcemia the dosage should be reduced The patient should never be allowed to continue treatment on his own initiative The greatest danger of all perhaps comes in taking

doses of vitamin D large enough to produce cumulative effects over a very long period of time Once the diagnosis of hypervitaminosis D is made the patient should be prohibited everything which tends to increase the blood calcium

TOM D SPIES

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Snake Venom Poisoning

Venomous serpents are particularly abundant in tropical and subtropical countries which are under intensive agricultural cultivation The ophidian population of such places is always augmented as a result of the increase in the number of rats mice and other rodents which accompanies the production of crops India Java Malaya southeastern Brazil southwestern United States eastern Mexico and the Central American republics since the advent of widespread cultivation may be cited among the highly snake infested regions of the world

Venomous snakes feeding on rodents are rather rare in forests or in wooded districts even in the tropics because in order to survive they must resist active competition on the part of many species of predatory animals both birds and mammals which also feed on rodents and live in woody sections

Etiology From a biological point of view most serpents must be considered *venomous* for on each side of the head they have a gland that yields a viscous secretion capable of producing toxic or destructive effects on animal tissues From a medical standpoint however only those ophidians are considered *veneniferous* which upon biting or stabbing are able to inject the secretion of their supralabial glands more or less deeply into the tissues of their prey or potential enemy

These snakes are all included in two groups which in ophiology are called Proteroglypha and Solenoglypha The Proteroglypha bear small fangs longitudinally grooved one on each side of the anterior upper jaw each fang is firmly implanted in the maxilla which is articulated with other skull bones The coral snakes are the only representatives of this group in America

The Solenoglypha bear rather large fangs hollow like a hypodermic needle in a series on each anterior aspect of their upper jaw of each series the foremost fang is the acting one the others being supplementary The ophidians of this group are the vipers which are of two kinds the more important being the pit vipers named after the hole or pit on each side of the head between the nostril and the eye Among the true pitless vipers the most dreaded species is the Gaboon viper which is provided with very voluminous venom glands and large fangs The pit vipers are found in the United States where they are represented by the copperhead the water moccasin and the rattlers of which there are some twelve species Of the rattlers the most venomous are the Florida rattler the Texas rattler the prairie rattler and the black tailed rattler In Latin America the most important pit vipers are the fer de lance or barba amarilla the cascabel or cascavel the surucucu or bushmaster the jararaca the jararacuçu and the urutu

The venom apparatus is made up of a gland a duct and an active fang on each side Physiologically the venom acts as a sort of saliva and serves both to facilitate the swallowing of the prey and to initiate the digestion of the prey s tissues through enzymic action The amount of venom a serpent can eject varies from a few drops to 2 ml the active constituents may weigh as much as 650 mg (exceptionally 1 gm)

Chemistry of Snake Venoms Venoms are composed chiefly of proteins including toxins and enzymes which are responsible for their toxicity The toxicity of a venom may be lost if it is treated by chemicals or exposed to both light and heat However venoms are little modified by glycerin which serves as the best means for their preservation in the field In the laboratory full stability can be achieved only when the venom is frozen and desiccated under high vacuum immediately after being obtained

from the snake and is subsequently kept in the dark and at low temperature *

For many years little was known of the chemical composition and the real nature of the toxic principles of venom Professor Karl Slotta and his associates working at the Instituto Butantan under my direction have confirmed the findings of Micheel and Jung as to the chemical nature of the venom active principles and are inclined to ascribe to the presence of 5 to 7 atoms of sulfur (bound to cystine) an important binding role in the large protein molecule of the neurotoxin giving it a peculiar specificity Moreover they have succeeded in isolating from the South American rattler s venom an active principle crotoxin which contains 18 amino acids at least and has a molecular weight of about 30 500 Crotoxin exerts both neurotoxic and hemolytic actions in the body and appears to be composed of two pharmacologically different substances (Neumann and Habermann) Another principle called crotamin has recently been isolated from South American rattler venom From the venom of the Indian cobra a purified enzyme different from neurotoxin has been obtained in crystalline form it represents the hemolytic principle of this venom being about thirty three times more potent than the latter

According to Singer and Kearney the yellow color found in most venoms particularly those of the Nearctic rattlers and the Neotropical species of Bothrops seems to be due to riboflavin the action of which is correlated with the presence of an enzyme λ amino acid oxidase

Pathological Physiology Every venom appears to have unique properties The individual physiological peculiarities are due to the variations in composition which are found among species even of the same genus Thus the venom of the South American rattler *Crotalus terrificus* acts very slowly upon the organism and produces nervous symptoms (blindness local paralyses and so forth) only after an incubation period of a few hours and never causes even local pain The venom of nearly all the North American rattlers (*Crotalus atrox adamanteus ruber molossus* and others) acts rather rapidly upon the body and causes marked swelling and other local symptoms in the virtual absence of any sign of nervous disturbances

The active constituents of snake venoms are usually classified as neurocytolysins hemolysins and hemocoagulins proteolysins and cytolysins

Neurocytolysins have a systemic effect are slow to act and affect the respiration and circulation or the vision and other specialized functions They are prevalent in the venom of the South American rattler and all the Western World coral snakes the Indian cobras the African mamba and others

Hemolysins acting on both the erythrocytes and the leukocytes complicate the local symptoms produced by proteolysins and cytolysins which act in the earlier stages of the poisoning and are responsible for the respiratory disturbances which sometimes appear during the later phases of the venenation By lysis of red cells hemolysins contribute to the reduction of the oxygen intake of the tissues They are particularly prevalent in the venom of the Indian cobra and daboia the Texas rattler the South American urutu and fer-de lance

Hemocoagulins act both on the coagulating and the anticoagulating mechanisms of the blood Some venoms have trypsin like enzymes and react with prothrombin to form thrombin while others bear papain like enzymes and react with fibrinogen to precipitate fibrin the result in both cases being blood coagulation In the former group may be included the venoms of the South American jararaca and fer de lance and some coral snakes in the latter group are the venoms not only of the Florida rattler and the South American cascavel but also of the South American jararaca and fer de lance Finally those venoms that prevent blood coagulation appear to destroy either prothrombin or fibrinogen or else they neutralize thrombin itself thus acting in the same manner as heparin This type of venin is secreted by such snakes as the American water moccasin the African puff adder the Texas rattler the Indian daboia and the European sand viper and a heparin like action is exerted by the Indian cobra venom

Proteolysins and *cytolysins* are the typical phlogogenous substances responsible for the local symptoms such as pain swelling discoloration necrosis and mutilation which follow the stab of certain vipers and pit vipers They are particularly noticeable in the secretion of such snakes as most North American rattlers the Latin Ameri

* From a biochemical standpoint the following powerful enzymes have already been recognized by electrophoresis in snake venoms serving both to complicate the action of the poison toxins and to induce harmful progressive chain effects on the tissue constituents proteases nucleotidases λ amino-acid oxidase hyaluronidase (spreading factor) phosphatases (including phospholipase A) and acetyl cholinesterase

can fer-de lance jararaca jararacuçu and urutu the Japanese habu the Asiatic and Malayan green pit viper and the Indian daboia By dissolving the tissue proteins proteolysins open the way for cytolysins which in turn are responsible for the de struction of the cell structure

Symptomatology The symptoms of ven enation vary widely according to the chem ical composition of the poison They may be briefly summarized as follows according to the species or groups of snakes

1 *Coral snakes* salivation and lacrima tion depression and somnolence trembling and convulsions—all resulting from the action of the chemical constituents of the venom on the autonomic nervous system The poisoning may result in death

2 *South American rattler* impairment of vision or complete blindness paralysis of both eyelids and eyeballs paralysis of peripheral muscles (especially about the neck which acts as though it were broken)—all caused by the action of the chemical principles on the neuromuscular apparatus finally a lesion of the lower nephron with occasional hematuria Death is usually the outcome

3 *Spectacled cobra* salivation and vom iting hemorrhages and fall of blood pres sure prostration blindness and somno-lence dyspnea apnea and death—all caused by the effect of the venom on the blood and the autonomic nervous system

4 *King cobra* dyspnea polypnea pro-fuse sweating and death resulting from the direct action of the venom on the central nervous system and the phrenic nerve end ings

5 *North American rattlers* local pain edema and discoloration followed by ecchy moses and phlyctenules blood destruction all through the affected tissues prostra tion nausea vomiting or diarrhea follow ing absorption of residues of both tissue and blood collapse and sometimes death

6 *Indian daboia* marked local swelling and tissue destruction profuse hemorrhages because of lack of blood clotting fall of blood pressure and collapse hematuria al buminuria anemia and emaciation some times resulting in death

7 *Latin American pit vipers* excluding the cascabel and the bushmaster exten sive local reaction with edema ecchymosis and adenitis thirst and diarrhea hemor rhages of the eyes ears mouth intestines or kidneys prostration exhaustion fol lowed sometimes by death The symptoms following the bite of the Japanese habu and most of the Asiatic and Malayan pit vipers are more or less comparable to these

Diagnosis The diagnosis of a case of venenation is based primarily on the cap-ture or examination of the snake that caused the bite and secondarily on the description of its characteristics by the vic tim The physician being acquainted with the local ophiological fauna must examine the patient thoroughly in order to establish his diagnostic conclusion The specificity of the treatment to be applied depends on the correctness of his findings Final diagnosis will be based chiefly on the discovery of puncture marks at the site of the alleged bite "

Prognosis and Death Rate The prognosis of snake poisoning is always grave when the patient is small or young when the amount of venom injected by the bite is large or when the snake fang happens to enter a vein thus forcing the poison di rectly into the circulation

It may happen that the serpent has re cently eaten or bitten an animal before biting a human being In this instance little venom may be present in the glands and the acci dent will be mild In contrast the serpent may be fullgrown or may have been quiet for a long time in such circumstances its glands will contain a large amount of secretion For this reason snake poisoning is usually more severe in early spring when the reptiles start crawling out from their winter retreats

In the event that symptoms develop rap-idly and the patient loses sight becomes unconscious or experiences a rapid fall in blood pressure the accident must be con sidered serious and the prognosis bad

The death rate depends directly upon the types of snakes prevailing in any region With species like the Latin American casca bel the Indian cobras and daboia and the African mamba whose venoms are ex tremely powerful or are secreted in amounts too great for human resistance the death rate is relatively high An average of 25 000 deaths occur annually in India from ophidic accidents the majority of which are due to the spectacled cobra In contrast there were but 14 fatal cases of poisoning in Europe all caused by local vipers from 1883 to 1892 In the Okinawan islands an annual average of about 225 persons used to be poisoned by the habu with a death rate of about 15 per cent

In this country statistics prepared by the Antivenin Institute of America seem to indicate that the yearly number of cases

of snake bite may amount to 2000 to 3000 the death rate varying from 10 to 35 per cent

Treatment The treatment of snake poisoning consists in the application of specific antivenins followed by additional measures when necessary if antivenins are unavailable local therapy should be applied

Antivenins are the only known agents capable of neutralizing venoms and arresting their harmful effects on the body Injections of these specific serums may be made hypodermically intramuscularly or intravenously (the patient being properly prepared against allergic reactions) according to the seriousness of the case

If the antivenin can be given at once or within the first two hours after the bite about half the dose should be injected immediately around the wound in order to prevent local destruction of the tissues by venom of the phlogogenic type such as that of the American and Oriental pit vipers and the daboia In late treated cases however this local application is not indicated In such cases and always in those in which the symptoms are severe intravenous injection of the specific antivenin is strongly advised

As to dosage the physician must remember that the age or weight of the victim of the bite is an important factor Its relation to the amount of serum is just the reverse of the usual rules for dosage In the case of ophiotoxosis the concentration of venom per kilogram of body weight is relatively greater in young or light persons (or animals) than in adult or heavy persons Therefore the smaller or lighter the person the greater and the more urgent the need for the antivenin When there is reason to believe that the venin inoculated by the serpent was of unusually large quantity or whenever the symptoms develop quickly and in severe form as for instance in children it is advisable to start with a double dose and repeat it at short intervals if the previous dose has not caused an amelioration of the symptoms For adults or heavy patients the usual dose is one to three syringes or ampules of 10 cc each The serum to be given may be either of the liquid type kept in the icebox for preservation of its potency or of the lyophilized type in which case the powder is first dissolved in the usual way

In all cases the victim should be watched for three to five hours after every injection and if his condition has not markedly improved within that time an additional injection should be made *

Special procedure to be carried out whenever specific serum or antivenin is not available

1 Apply a ligature or tourniquet above the bite site This should be applied tightly at first but must be partially released for a few seconds at five to ten minute intervals so as to maintain the necessary circulation in the limb There is no particular advantage in making an incision or in applying permanganate of potassium in solution or crystals or any of the other chemical agents empirically recommended for this purpose In fact it is advisable to avoid any further mutilation or injury that might facilitate the development of tetanus gas gangrene or secondary infection and thus complicate the patient s condition Exception to this rule may be made only in those cases with large swelling and discoloration followed by severe general symptoms such as result from a bite by the Indian daboia or the majority of the North American rattlers The venoms of these serpents are both hemolytic and noncoagulant and cause intense edema and extravasations of blood The toxins absorbed by the lymph vessels and at the site of their inoculation form a poisonous substance (*lysocythin* due to the splitting action of phospholipase A on lecithin) from the extravasated blood For this reason it is advisable in these particular instances to make a series of incisions around the puncture marks left by the snake and to apply strong suction by means of a hydraulic pump (a good vacuum rubber bulb pump may be used) attempting to extract the lysocythin together with the residues of destruction of both blood and tissues

2 Strychnine caffeine black coffee or strong tea may be given to the patient if symptoms of weakness and giddiness develop

* Since some venoms particularly those causing local hard edema and late tissue destruction appear to act also through the so-called anti spreading factor (hyaluronic acid) which hinders the absorption of the antivenin given around the site of the bite it is advisable previous to injecting the specific serum to mix with its dose a certain amount (about 1 to 2 mg) of *hyaluronidase* and administer the mixture subcutaneously In this case in order to prevent the rapid dissemination throughout the system of the toxic derivatives of the venom held up by the swollen tissues it is necessary to take special precautions with the patient by giving him an extra dose of antivenin with ephedrine intravenously and by watching his heart and kidney functions

3 It is important to bear in mind that in late and severe cases complicated by profuse bleeding symptoms of liver injury low blood pressure or dehydration rapid relief may sometimes be obtained from the intravenous administration of saline followed by glucose solution or Ringer sodium lactate solution

Prophylaxis The consequences of venenation may be prevented in two ways first by avoiding snake bites second by properly treating the accident

The prevention of snake bites may be achieved by wearing heavy shoes and leather leggings whenever one goes into a snake infested district and by avoiding the use of the bare hands in climbing a rock or a ledge where snakes may be encountered

AFRANIO DO AMARAL

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Food Poisoning

INTRODUCTION

Food poisoning may occur from the ingestion of a diverse group of inciting agents The literature contains records of many outbreaks of gastrointestinal illnesses in which the inciting agent given is in error Some of the errors in the earlier reports were due to lack of knowledge concerning the inciting agents For example Salmonella organisms have been assigned as the cause of several outbreaks of food poisoning which were obviously due to staphylococci The term "ptomaine poisoning" is still used in newspaper reports of outbreaks of food poisoning and unfortunately is occasionally used by the medical profession This term came into use soon after the word was coined by the Italian toxicologist Selmi in 1870 Much work has been done with toxic products extracted from foods and tested by parenteral injection into animals Animals receiving injections of these materials frequently manifested shock and developed diarrhea and labored respiration preceding death Many filtrates prepared from broth cultures of Salmonella bacilli are toxic when injected intravenously into rabbits and other experimental animals The peculiar feature of this toxicity is that it is limited to *parenteral* injections—the same material often is without any effect when given by *mouth* This situation also applies to the products of putrefaction among which are the amines The "ptomaine" theory would never have gained prominence if experimental animals had reacted similarly to man when fed foods implicated in outbreaks of food poisoning Perhaps the majority of so-called "ptomaine food poisoning" outbreaks may be attributed to staphylococci There is abundant evidence to indicate that putrefied foods in the absence of food poisoning agents are without ill effect when ingested It is well known for example that the Eskimo considers putrefied seal meat a delicacy

Food Allergy Some persons are allergic to certain items of food which though wholesome to most people may act as poisons to those who are sensitized to them One example is the case of the *Vicia faba* bean which is cultivated extensively in New York New Jersey Illinois and California and is a staple article of diet particularly with people of Italian extraction Sensitization to the bean appears to be on a hereditary basis since in certain families every member for generations has been reported severely affected Therefore susceptibility varies and certain persons after years of eating the beans with impunity may suffer a single severe attack and none subsequently Illness may follow inhalation of pollen from the blossoming plant or within an hour after eating the beans The illness is characterized by acute febrile anemia with jaundice hematuria and hemoglobinuria

A number of chemicals have been taken by mistake or accident and thus have been implicated in food poisoning Usually illnesses from chemical poisoning occur within a few minutes to an hour or two after ingesting the chemical The poisons include antimony arsenic barium carbonate cadmium *sodium fluoride lead* methyl chloride mercury nitrates and zinc Of this list *cadmium* and sodium fluoride have been most commonly involved If acid

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Treatment The treatment of snake poisoning consists in the application of specific antivenins followed by additional measures when necessary if antivenins are unavailable local therapy should be applied

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As to dosage the physician must remember that the age or weight of the victim of the bite is an important factor Its relation to the amount of serum is just the reverse of the usual rules for dosage In the case of ophiotoxosis the concentration of venom per kilogram of body weight is relatively greater in young or light persons (or animals) than in adult or heavy persons Therefore the smaller or lighter the person the greater and the more urgent the need for the antivenin When there is reason to believe that the venin inoculated by the serpent was of unusually large quantity or whenever the symptoms develop quickly and in severe form as for instance in children it is advisable to start with a double dose and repeat it at short intervals if the previous dose has not caused an amelioration of the symptoms For adults or heavy patients the usual dose is one to three syringes or ampules of 10 cc each The serum to be given may be either of the liquid type kept in the icebox for preservation of its potency or of the lyophilized type in which case the powder is first dissolved in the usual way

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toxin There are five toxigenic types A B C D and E Of these five three have been found to cause food poisoning in man namely types A B and rarely E The symptoms produced by all types of toxin are the same but the antitoxin differs for each type The toxin appears to interfere with the production of acetylcholine

Symptoms In some but not all persons the central nervous system symptoms characteristic of botulism are preceded by an active digestive disturbance and vomiting In general nausea and vomiting occur in less than twenty four hours and appear to bear some relation to the degree of spoilage and to the amount of incriminated food consumed Although dehydration may develop early in some cases constipation is present in the later stages of the disease Typical symptoms usually appear in twelve to thirty six hours In many instances the earliest symptom is a peculiar lassitude or fatigue sometimes associated with dizziness or headache and attributed to constipation Double vision or diplopia may occur early Photophobia nystagmus and vertigo are occasionally recorded Difficulty in swallowing and in speech is observed later in the disease A sense of constriction of the throat is described occasionally Usually the tongue is coated and swollen Paralysis of the pharyngeal muscles occurs in fatal cases and it is not uncommon for fluids to be regurgitated through the nose and mouth The muscles in the neck are often weakened and there may be muscular incoordination There is no retention of urine although the amount secreted may be small since patients cannot swallow and proper fluid balance is not maintained The temperature is usually normal or subnormal Bronchopneumonia may develop because of aspiration of mouth contents The pulse may be normal but often becomes rapid in the later stages even though the temperature remains normal The respiration occasionally becomes irregular and Cheyne Stokes breathing has been observed just before death The blood pressure is usually normal and no abnormalities in type or number of blood cells have been found Death results from respiratory failure Life has often been sustained for several hours by artificial respiration The Drinker respirator has been used in several cases but without success The duration of illness in fatal cases is usually three to six days after ingestion of the poisonous food

Diagnosis The diagnosis of botulism can usually be made from the symptoms Confusion has sometimes occurred in cases of chemical poisoning involving methyl chloride and sodium fluoride In acute sodium fluoride poisoning vomiting abdominal pains and diarrhea are marked The paralysis of certain groups of muscles (eye muscles facial muscles hand extensors and those of the lower extremities) contraction of the pupils and paresthesia in the extremities have led to confusion with botulism In botulism the gastrointestinal symptoms are mild if present and the diplopia aphonia and labored breathing are pronounced Methyl chloride poisoning is characterized by progressive drowsiness mental confusion stupor nausea pain in the abdomen and vomiting In severe cases convulsions and cyanosis alternating with coma have led to confusion with botulism In botulism the sensorium is usually clear up to the time of death In the majority of cases there is a history of ingestion of home-canned foods which frequently may have had a rancid or slightly putrefactive odor or taste In the laboratory diagnosis blood taken from patients occasionally may contain sufficient toxin to cause the death of mice into which 1 ml of serum has been injected intraperitoneally If the food has been discarded and fed to chickens limberneck may develop in the chickens causing death Suspected items of food should be sent to the laboratory and examined for toxin and/or the presence of *C botulinum* The toxin can be typed in the laboratory using the specific antitoxin

Prognosis The mortality from botulism in the United States is approximately 65 per cent but in Europe it is much lower When a large dose of toxin is ingested symptoms occur within a short time usually less than twenty four hours In nonfatal cases the symptoms subside slowly and usually several weeks elapse before all residual signs of the disease have disappeared and recovery is complete

Treatment The treatment of botulism is unsatisfactory The sooner the disease is recognized the better the opportunity for the physician to treat those more fortunate persons who have eaten less of the poisonous food and have not manifested symptoms early Since the majority of cases are due to type A or B it is advisable to give polyvalent antitoxin for these two types In the presence of symptoms antitoxin is frequently given too late for it cannot repair the damage already done to the patient by the toxin Antitoxin should be given even though the disease is advanced in the hope of neutralizing any toxin which

foods are placed in cadmium plated utensils such as pitchers or ice trays in mechanical refrigerators sufficient cadmium is dissolved to cause abdominal cramping severe diarrhea and vomiting within fifteen to thirty minutes afer eating or drinking the foods or beverages *Sodium fluoride* is widely used to exterminate cockroaches from food establishments Since it is a white powder it has frequently been mistaken for baking powder soda or flour Illness usually follows within a few minutes to two hours and is characterized by an acute poisoning—vomiting (often hemorrhagic) diffuse abdominal pains and diarrhea occur with great constancy convulsions tonic or clonic spasms of certain muscle groups paresis of certain groups of muscles (eye muscles facial muscles hand extensors and those of lower extremities) hiccup and contraction of pupils may occur Paresthesia occasionally is present in extremities and has led to confusion with botulism Arsenic lead and mercury poisoning are discussed at length elsewhere in this book under their respective titles

Shellfish poisoning has occurred along the West Coast in central California with a sprinkling of severe outbreaks from Juneau Alaska to southern California the Gulf of California and Mexico In the eastern part of North America it has been found due to shellfish from the Bay of Fundy The illnesses have been traced to the food of the shellfish Gonyaulax in the cases on the West Coast to *Gonyaulax catanella* Chemical studies have been made of the poison and some preparations have been made which have a toxicity greater than 1 MU per microgram The MU is the amount of mussel poison which when dissolved in 1 ml of water and injected intraperitoneally into a 20 gm white mouse will cause death in fifteen minutes Shellfish poisoning is characterized by respiratory paralysis Symptoms vary from trembling about the lips to complete loss of power in the muscles of the neck The illness develops within five to thirty minutes and longer after eating the poisoned mussels

Plant Poisons Of the more common poisonings due to plants snakeroot poisoning mushroom poisoning ergotism and water hemlock poisoning may be mentioned The most poisonous of the mushrooms is *Amanita phalloides* It has been reported that two or three of these mushrooms may be sufficient to cause illness and death in the adult A patient with mushroom poisoning has hypoglycemia which may be accompanied by convulsions severe abdominal pain intense thirst nausea retching vomiting and profuse watery evacuations The illness occurs within six to fifteen hours after ingestion of the poisonous mushrooms *Ergot poisoning* has occurred from eating rye meal or rye bread prepared from diseased rye containing a fungus *Claviceps purpurea* and may develop after several meals of diseased rye The symptoms are drowsiness headache giddiness painful cramps of the limbs and itching of the skin In the more severe cases gangrene may occur involving especially the fingers and toes and occasionally the ears and nose *Water hemlock poisoning* occurs when the leaves and roots of the water hemlock are eaten The onset of illness comes one to two hours after ingestion and is characterized by nausea vomiting and convulsions

In all instances of poisoning it is important to recognize the type in order to prevent the occurrence of further cases Often there is no specific treatment the vomiting and diarrhea serve the useful purpose of eliminating the poison which is not already absorbed Symptomatic treatment should be given and in the types of poisoning characterized by severe vomiting and diarrhea parenteral fluids should be administered if dehydration and loss of electrolytes in the body have been excessive

BACTERIAL FOOD POISONING

Food poisoning from bacteria may be divided into two general categories In the first toxins are preformed in the food by the growth of microorganisms and the illnesses are due to the *toxins* and not to the ingested *organisms* In the other category the living *organisms* alone are responsible for the illnesses filtrates or heated dead cultures being without effect

PREFORMED TOXINS

Botulism

Today most outbreaks of botulism occur from the use of home canned foods In the United States ten to fifteen outbreaks occur annually The term "botulism originated from the word botulismus meaning a sausage and was coined by physicians in southern Germany in the beginning of the nineteenth century *The causative agent Clostridium botulinum* is a large gram positive rod shaped organism which is an anaerobic spore former The organism is a natural saprophyte and is commonly found in the soil The spores are very heat resistant and in foods that are not properly processed they may germinate and produce

toxin There are five toxigenic types A B C D and E Of these five three have been found to cause food poisoning in man namely types A B and rarely E The symptoms produced by all types of toxin are the same but the antitoxin differs for each type The toxin appears to interfere with the production of acetylcholine

Symptoms In some but not all persons the central nervous system symptoms characteristic of botulism are preceded by an active digestive disturbance and vomiting In general nausea and vomiting occur in less than twenty four hours and appear to bear some relation to the degree of spoilage and to the amount of incriminated food consumed Although dehydration may develop early in some cases constipation is present in the later stages of the disease Typical symptoms usually appear in twelve to thirty six hours In many instances the earliest symptom is a peculiar lassitude or fatigue sometimes associated with dizziness or headache and attributed to constipation Double vision or diplopia may occur early Photophobia nystagmus and vertigo are occasionally recorded Difficulty in swallowing and in speech is observed later in the disease A sense of constriction of the throat is described occasionally Usually the tongue is coated and swollen Paralysis of the pharyngeal muscles occurs in fatal cases and it is not uncommon for fluids to be regurgitated through the nose and mouth The muscles in the neck are often weakened and there may be muscular incoordination There is no retention of urine although the amount secreted may be small since patients cannot swallow and proper fluid balance is not maintained The temperature is usually normal or subnormal Bronchopneumonia may develop because of aspiration of mouth contents The pulse may be normal but often becomes rapid in the later stages even though the temperature remains normal The respiration occasionally becomes irregular and Cheyne Stokes breathing has been observed just before death The blood pressure is usually normal and no abnormalities in type or number of blood cells have been found Death results from respiratory failure Life has often been sustained for several hours by artificial respiration The Drinker respirator has been used in several cases but without success The duration of illness in fatal cases is usually three to six days after ingestion of the poisonous food

Diagnosis The diagnosis of botulism can usually be made from the symptoms Confusion has sometimes occurred in cases of chemical poisoning involving methyl chloride and sodium fluoride In acute sodium fluoride poisoning vomiting abdominal pains and diarrhea are marked The paralysis of certain groups of muscles (eye muscles facial muscles hand extensors and those of the lower extremities) contraction of the pupils and paresthesia in the extremities have led to confusion with botulism In botulism the gastrointestinal symptoms are mild if present and the diplopia aphonia and labored breathing are pronounced Methyl chloride poisoning is characterized by progressive drowsiness mental confusion stupor nausea pain in the abdomen and vomiting In severe cases convulsions and cyanosis alternating with coma have led to confusion with botulism In botulism the sensorium is usually clear up to the time of death In the majority of cases there is a history of ingestion of home canned foods which frequently may have had a rancid or slightly putrefactive odor or taste In the laboratory diagnosis blood taken from patients occasionally may contain sufficient toxin to cause the death of mice into which 1 ml of serum has been injected intraperitoneally If the food has been discarded and fed to chickens limberneck may develop in the chickens causing death Suspected items of food should be sent to the laboratory and examined for toxin and/or the presence of C *botulinum* The toxin can be typed in the laboratory using the specific antitoxin

Prognosis The mortality from botulism in the United States is approximately 65 per cent but in Europe it is much lower When a large dose of toxin is ingested symptoms occur within a short time usually less than twenty four hours In nonfatal cases the symptoms subside slowly and usually several weeks elapse before all residual signs of the disease have disappeared and recovery is complete

Treatment The treatment of botulism is unsatisfactory The sooner the disease is recognized the better the opportunity for the physician to treat those more fortunate persons who have eaten less of the poisonous food and have not manifested symptoms early Since the majority of cases are due to type A or B it is advisable to give polyvalent antitoxin for these two types In the presence of symptoms antitoxin is frequently given too late for it cannot repair the damage already done to the patient by the toxin Antitoxin should be given even though the disease is advanced in the hope of neutralizing any toxin which

foods are placed in cadmium plated utensils such as pitchers or ice trays in mechanical refrigerators sufficient cadmium is dissolved to cause abdominal cramping severe diarrhea and vomiting within fifteen to thirty minutes afer eating or drinking the foods or beverages *Sodium fluoride* is widely used to exterminate cockroaches from food establishments Since it is a white powder it has frequently been mistaken for baking powder soda or flour Illness usually follows within a few minutes to two hours and is characterized by an acute poisoning—vomiting (often hemorrhagic) diffuse abdominal pains and diarrhea occur with great constancy convulsions tonic or clonic spasms of certain muscle groups paresis of certain groups of muscles (eye muscles facial muscles hand extensors and those of lower extremities) hiccup and contraction of pupils may occur Paresthesia occasionally is present in extremities and has led to confusion with botulism Arsenic lead and mercury poisoning are discussed at length elsewhere in this book under their respective titles

Shellfish poisoning has occurred along the West Coast in central California with a sprinkling of severe outbreaks from Juneau Alaska to southern California the Gulf of California and Mexico In the eastern part of North America it has been found due to shellfish from the Bay of Fundy The illnesses have been traced to the food of the shellfish Gonyaulax in the cases on the West Coast to *Gonyaulax catanella* Chemical studies have been made of the poison and some preparations have been made which have a toxicity greater than 1 MU per microgram The MU is the amount of mussel poison which when dissolved in 1 ml of water and injected intraperitoneally into a 20 gm white mouse will cause death in fifteen minutes Shellfish poisoning is characterized by respiratory paralysis Symptoms vary from trembling about the lips to complete loss of power in the muscles of the neck The illness develops within five to thirty minutes and longer after eating the poisoned mussels

Plant Poisons Of the more common poisonings due to plants snakeroot poisoning mushroom poisoning ergotism and water hemlock poisoning may be mentioned The most poisonous of the mushrooms is *Amanita phalloides* It has been reported that two or three of these mushrooms may be sufficient to cause illness and death in the adult A patient with mushroom poisoning has hypoglycemia which may be accompanied by convulsions severe abdominal pain intense thirst nausea retching vomiting and profuse watery evacuations The illness occurs within six to fifteen hours after ingestion of the poisonous mushrooms *Ergot poisoning* has occurred from eating rye meal or rye bread prepared from diseased rye containing a fungus *Claviceps purpurea* and may develop after several meals of diseased rye The symptoms are drowsiness headache giddiness painful cramps of the limbs and itching of the skin In the more severe cases gangrene may occur involving especially the fingers and toes and occasionally the ears and nose *Water hemlock poisoning* occurs when the leaves and roots of the water hemlock are eaten The onset of illness comes one to two hours after ingestion and is characterized by nausea vomiting and convulsions

In all instances of poisoning it is important to recognize the type in order to prevent the occurrence of further cases Often there is no specific treatment the vomiting and diarrhea serve the useful purpose of eliminating the poison which is not already absorbed Symptomatic treatment should be given and in the types of poisoning characterized by severe vomiting and diarrhea parenteral fluids should be administered if dehydration and loss of electrolytes in the body have been excessive

BACTERIAL FOOD POISONING

Food poisoning from bacteria may be divided into two general categories In the first toxins are preformed in the food by the growth of microorganisms and the illnesses are due to the *toxins* and not to the ingested *organisms* In the other category the living *organisms* alone are responsible for the illnesses filtrates or heated dead cultures being without effect

PREFORMED TOXINS

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large numbers of the heat killed cocci are observed *Usually there is a history of the* food having been kept at a warm temperature for a period of several hours before being cooked and served

When individuals rather than groups of people are taken ill with symptoms resembling those of staphylococcal food poisoning it is important first to eliminate other possible causes of the illness such as gall bladder disease appendicitis *certain forms* of intestinal allergy onset of infectious diseases and functional bowel distress associated with emotional upsets Enterotoxin may be produced by staphylococci in the bodies of patients under treatment with large doses of broad spectrum antibiotics The diagnosis of staphylococcal food poisoning must be seriously considered when *several members of a family or a group* suddenly become ill with symptoms of vomiting diarrhea abdominal cramps and prostration coming on within two and one half to three hours after a meal Enteric infections caused by bacteria or viruses are not of the explosive nature characterizing staphylococcal food poisoning and the illnesses appear over a longer period of time

Prognosis In general the acute illness in staphylococcal food poisoning usually does not persist longer than five hours although anorexia and diarrhea may continue for several days after the acute attack Fatalities are rare A death occurred in one member of a family made ill by contaminated beef and in one outbreak two children three and four years old died within twenty four hours after each drank 250 ml of milk from a goat suffering from acute suppurative mastitis Other deaths have been reported in young children and aged or debilitated persons

Treatment *Vomiting and diarrhea are* usually severe therefore it is not necessary to empty the stomach with a stomach pump or to give cathartics to free the gastrointestinal tract of enterotoxin Prostration occurs in severe cases and the blood pressure may fall precipitously The symptoms of shock are due to loss of body fluids and electrolytes resulting in decreased circulating blood volume and should be corrected immediately by the administration of saline solutions parenterally The amount of fluid to be given should be governed by the age of the patient and the severity of the vomiting and diarrhea There is no specific drug or serum therapy

Prevention Since staphylococci are abundant in nature and commonly present in the secretions of the nose and throat and in purulent lesions of the skin it is impossible *to exclude them from foods exposed to the* air Staphylococci will grow in the presence of amounts of salt and sugars which are inhibitory to the common enteric bacilli Because of this fact many foods which the housewife would regard as preserved might provide a good medium for staphylococci When staphylococci grow in food there is no perceptible off flavor or taste to indicate *their presence It has been shown experimentally* that enterotoxin is not formed in periods up to four weeks at temperatures maintained by the ordinary mechanical refrigerators even though other conditions necessary for enterotoxin production are fulfilled Therefore at the present time the best control of staphylococcal food poisoning consists in adequate refrigeration of *perishable foods*

LIVING ORGANISMS

Salmonella Food Poisoning

Since Salmonella infections are discussed elsewhere in this book only brief reference will be made here to the role of Salmonella in food poisoning Strains of Salmonella have long been associated with food poisoning and many theories have been proposed to implicate them as causative agents when bacteriological studies have been negative or inconclusive An attempt has been made to explain some outbreaks on the basis that these organisms produce endotoxins which survive heat treatments that would destroy the living Salmonella Most of the work with endotoxins *involved parenteral injections* into experimental animals Human volunteers *fed* filtrates and heat killed cultures of Salmonella which are toxic by parenteral injections into animals have not become ill —only *living organisms* have caused illness in man If symptoms are caused by endotoxins the living organisms undoubtedly must invade the tissue to by pass the natural barrier of the gastro*intestinal tract In* Salmonella infections characterized by acute gastrointestinal disturbances the onset of symptoms may vary from seven to seventy two hours after contaminated *food has been eaten*

Microorganisms in Relation to Food Poisoning

Although *the role of enterococci* in food poisoning has not been clearly established a number of food poisoning outbreaks have been described involving specific items of food which contained per gram hundreds of

is not already fixed in the tissues At least 50 000 units of antitoxin should be given intramuscularly after the patient has been tested for serum hypersensitivity and if necessary desensitized

It is important that other measures be taken in addition to specific treatment with antitoxin The fluid balance of the body should be maintained and in the presence of pharyngeal paralysis which occurs early fluids should be administered parenterally The taking of fluids or food by mouth should be discouraged when pharyngeal paralysis is marked in order to avoid the danger of aspiration pneumonia Saliva should be expectorated or aspirated from the throat in such cases The patient should be kept quiet in restful surroundings and encouraged to avoid even the slightest unnecessary movement In outbreaks of botulism involving several persons those who have only tasted the food or eaten sparingly of it usually do not exhibit symptoms until some time after those who have eaten generously of the poisonous food In such cases antitoxin should prove of great prophylactic value

Staphylococcal Food Poisoning

Definition Staphylococcal food poisoning also is caused by a toxin formed in the food before ingestion In the United States it is probably the most common of all food poisonings Since it is not a reportable disease the number of cases occurring annually is unknown It is an ailment which involves most persons at one time or another during their lives and no great attention is paid to it unless large groups of people are attacked such as at banquets encampments or in public institutions

Etiology Although the relation of staphylococci to foods implicated in this type of food poisoning has been known since 1884 staphylococcal food poisoning was not generally recognized until 1930 This failure to recognize the disease was due to the fact that when implicated foods and cultures made from them were fed to experimental animals no illness followed Unfortunately man appears to be peculiarly susceptible to the poison although extremely potent preparations cause vomiting and diarrhea when fed to kittens and monkeys (*Macaca mulatta*) However portions of enterotoxin containing food which cause serious illness in man may be fed to these animals without ill effect Not all strains of staphylococci produce enterotoxin and it is probable that only a few of the total strains in nature have this property The enterotoxin has been shown to develop within as short a period as four to five hours when food is kept at 86° F Unlike diphtheria botulinum and tetanus toxins it is relatively heat stable and has caused illness in a human volunteer after having been boiled for thirty minutes A wide variety of foods have been implicated including milk Cheddar cheese ice cream cream filled bakery goods rapid cured hams potato salad dried beef sausage chicken gravy tongue sandwiches hollandaise sauce liver sausage pressed pickled beef bread pudding and chicken salad

Symptoms Symptoms of staphylococcal food poisoning usually appear within about three hours although occasionally they developed one to six hours after ingestion of food containing enterotoxin The incubation period is influenced by the amount of enterotoxin consumed and the susceptibility of the person The first symptom observed is salivation which is subsequently followed by nausea vomiting retching abdominal cramps prostration and diarrhea In severe cases blood and mucus have been observed in the stools and vomitus In mild cases nausea and vomiting without diarrhea may occur or there may be cramps and diarrhea without vomiting Muscular cramps headache and sweating often occur when symptoms are moderately severe In severe poisoning marked prostration accompanies the vomiting and diarrhea and symptoms of shock have been observed A few fatal cases have occurred usually in the very young the aged or the debilitated As a rule the acute symptoms are of short duration and generally subside after five or six hours

Diagnosis The short interval of time between the eating of the incriminated food and the onset of symptoms is one of the most characteristic features of staphylococcal food poisoning If a list of foods served at the previous meal is available the various food items can be tabulated for those made ill as well as those who were not ill With such a list it is often possible to implicate one item of food as a common denominator The suspected food should be sent to the laboratory for a bacteriological examination Usually implicated foods contain enormous numbers of staphylococci However it must be remembered that the enterotoxin is not destroyed by boiling In some outbreaks the food item has been bacteriologically sterile although enterotoxin was present In such instances if the food is smeared on slides stained and examined microscopically

Deficiency Diseases

Introduction

Among primitive forms of life there are many species which live and grow on extremely simple diets If they are endowed with photosynthetic capacity carbon dioxide may serve as the sole required source of carbon Many nonphotosynthesizing microorganisms require only a single organic compound such as glucose for their nutrition Such forms are said to be *autotrophic* and for autotrophic bacteria there are no essential amino acids no vitamins

There is no evidence that the metabolic pathways in primitive autotrophs are any simpler than are the corresponding pathways in higher organisms The same kind of array of nucleotides amino acids lipids and proteins can be demonstrated in the primitive forms of life as in the tissues of the mammalian organism The difference is exemplified by the fact that niacin is synthesized by the autotroph at a rate compatible with its needs whereas the heterotrophic mammal has lost this ability and must ingest niacin to replenish its supply of pyridine nucleotide required for survival

The *heterotrophic* state *i e* the requirement for a complex diet if the organism is to survive and grow stems from the loss presumably by mutation of the capacity to synthesize from available dietary sources one or more necessary cellular ingredients The occurrence of such mutations has repeatedly been observed especially in *Neurospora crassa* cultures of the autotrophic wild strain have upon irradiation been found to generate daughter cells which require one or another amino acid or vitamin for further growth In many cases it has further been shown that the defect in such a vitamin requiring mutant results from the loss of a specific enzyme activity present in the parental wild type which participates in the synthesis of the vitamin in question The complex dietary requirements of man and other animals may be pictured as the results of mutations with consequent disappearance of certain enzyme-catalyzed reactions involved in the biosynthesis of what we call vitamins or essential amino acids Stated in another way any important organic compound of animal tissue may become a vitamin when and if an animal loses the capacity to synthesize that compound or to synthesize it at the required rate Thus scurvy and beriberi become inborn errors of metabolism " differing from other metabolic defects such as sickle cell anemia galactosemia or alkaptonuria in two important regards First the enzyme defects which result in beriberi or scurvy are universally present throughout the human species Second the manifestations of disease are readily controlled by dietary supplementation

In at least one instance the specific enzyme defect which leads to manifestations of disease when a vitamin is lacking in the diet has been pin pointed Of the steps D glucose ⟶ D-glucuronolactone ⟶ L gulonolactone ⟶ L ascorbic acid over which ascorbate synthesis proceeds in the rat and many other species it is the last step which cannot be accomplished in man and in the guinea pig Because of this absolute lack of a requisite enzyme ascorbic acid becomes vitamin C for man and the guinea pig In most other species including the rat lack of ascorbic acid in the diet produces no disease and ascorbic acid is not a vitamin

A somewhat different condition is seen in Addisonian anemia Here the metabolic error is apparently not inborn but is none the less real The symptoms and signs which result are readily controlled by ad

millions of *Streptococcus faecalis* a normal inhabitant of the human intestine Human volunteers fed either the item of food or cultures prepared from the food have in many instances had symptoms similar to those involved in the outbreaks Filtrates or heat killed cultures have failed to produce symptoms when fed to human volunteers Many volunteers who were fed cultures which were under laboratory cultivation for long periods of time also have failed to become ill Since *S faecalis* has been shown to decarboxylate tyrosine leaving an appreciable amount of tyramine in the food it was postulated that perhaps the tyramine was responsible for the symptoms However human volunteers who were fed tyramine in amounts as large as 1 gm have remained well The symptoms of this type of food poisoning are generally mild and are characterized by nausea sometimes vomiting colicky pains and diarrhea developing within two to eighteen hours after the incriminated food has been eaten and usually subsiding within a few hours thus requiring no specific treatment In these outbreaks a number of different types of foods have been involved such as Vienna sausage beef croquettes turkey dressing evaporated milk dried eggs charlotte russe roast beef and ham bologna

Bacillus cereus and *Clostridium perfringens* have been reported in outbreaks of food poisoning causing illnesses identical to that described for enterococci

G M DACK

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ministration of vitamin B_{12}, suggesting that this disease may be classified as a deficiency state It may be noted however that the patient diagnosed as having Addisonian anemia under proper control with vitamin B_{12} still has his disease The defect which makes this patient unusually dependent upon a supply of exogenous vitamin is still present and he is described as having Addisonian anemia in remission Here the name of the disease attaches to the underlying defect not to the presence or absence of signs and symptoms According to this convention the entire healthy human population could be described as having scurvy beriberi pellagra etc all in remission

The proper design of a human diet requires the consideration of a number of factors Among these the total caloric requirement must be met The ratio of carbohydrate to fat must exceed that level which will result in dietary ketosis An adequate supply of nitrogenous materials in the form of proteins must be insured In addition there are a number of requirements for specific elements or compounds which are listed in the accompanying table These comprise some nine to thirteen elements eight to ten amino acids and eleven to sixteen compounds which may be classified as vitamins Included in this list are all the known organic compounds which are needed for survival and health of the mammal and for which no adequate synthetic routes are available in man

Whereas the daily requirements for essential amino acids in man are measured in hundreds of milligrams or in grams the corresponding requirements for the vitamins are measured in milligrams or in micrograms From this fact it could be inferred that the vitamins the so called micronutrients are not necessarily destroyed by the essential reactions wherein they participate that their function is in some sense catalytic

For some but not for all the vitamins important catalytic roles can be defined Thiamine undergoes conversion to thiamine pyrophosphate which serves as a coenzyme in the oxidative decarboxylation of pyruvic acid as well as in the transketolase reaction Riboflavin enters into flavin adenine dinucleotide and flavin mononucleotide both of which are coenzymes for various essential electron transferring reactions Pyridoxine contributes to pyridoxal phosphate the coenzyme in numerous transamination reactions whereas niacin is needed to generate diphosphopyridine nucleotide and triphosphopyridine nucleotide the cofactors of the several dehydrogenases Folic acid has been shown to participate coenzymatically in various biological transfers of formyl residues and pantothenic acid is an essential part of coenzyme A an activating cofactor of the acetyl and other acyl groups The best known function of vitamin A is not strictly catalytic but relates to the very economical cyclical process whereby radiant energy is transduced into a nerve impulse at the retina For several of the vitamins specific chemical functions cannot be assigned at this time

Nutrients Essential for Man*

DEFINITELY ESTABLISHED	PROBABLE
Elements	Elements
Sodium	Zinc
Chlorine	Copper
Potassium	Fluorine
Iron	Molybdenum
Calcium	
Phosphorus	
Iodine	
Manganese	
Magnesium	
Amino Acids	
Arginine**	
Histidine**	
Threonine	
Phenylalanine	
Valine	
Leucine	
Isoleucine	
Methionine	
Tryptophan	
Lysine	
Vitamins	Vitamins
Thiamine	Pantothenic Acid
Riboflavin	Biotin
Pyridoxine	Inositol
Niacin†	Polyunsaturated fatty acids
Folic acid	Vitamin E
Vitamin B_{12}	
Ascorbic acid	
Vitamins A D** and K	
Choline‡	

* Adapted from White A Handler P Smith E L and Stetten D Jr Principles of Biochemistry New York McGraw Hill Book Co Inc 1954 p 1002

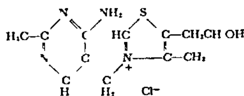
** Unnecessary for maintenance of adults but probably necessary for normal growth of children

† Requirement may be furnished by synthesis from dietary tryptophan

‡ Requirement may be furnished by synthesis from dietary methionine

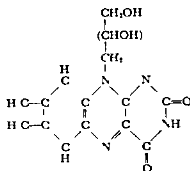
VITAMIN

RELATED COFACTOR



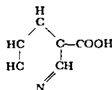
Thiamine chloride

Thiamine pyrophosphate (Cocarboxylase)

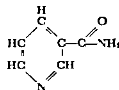


Riboflavin

Flavin adenine dinucleotide (FAD)
Flavin mononucleotide (FMN)

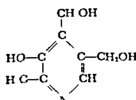


Niacin

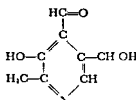


Nicotinamide

Diphosphopyridine nucleotide (DPN)
Triphosphopyridine nucleotide (TPN)

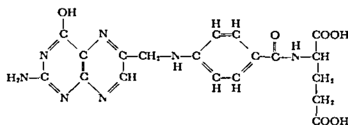


Pyridoxine



Pyridoxal

Pyridoxal phosphate

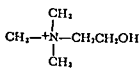


Folic acid

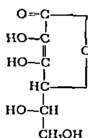
Citrovorum factor

FIG 49 Structural formulas of vitamins

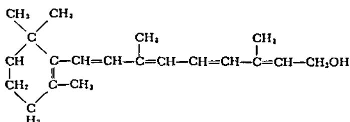
VITAMIN | RELATED COFACTOR



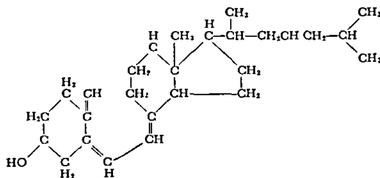
Choline chloride



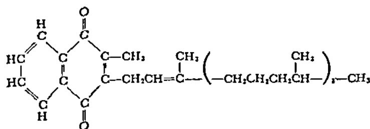
L-Ascorbic acid



Vitamin A₁



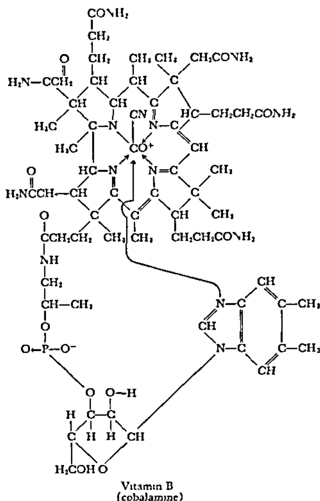
Vitamin D₃



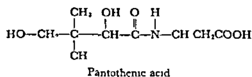
Vitamin K₁

FIG 49 Structural formulas of vitamins (*continued*)

VITAMIN | RELATED COFACTOR

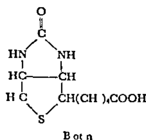


Vitamin B (cobalamine)



Pantothenic acid

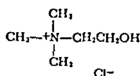
Coenzyme A



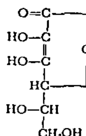
Biotin

Fig 49 Structural formulas of vitamins (*continued*)

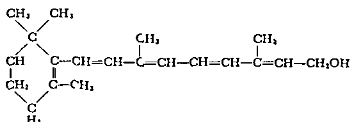
VITAMIN | RELATED COFACTOR



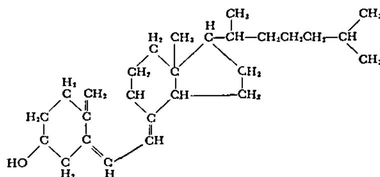
Choline chloride



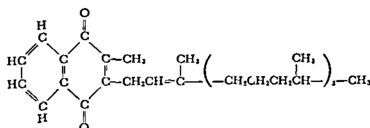
L-Ascorbic acid



Vitamin A_1



Vitamin D_3



Vitamin K_1

Fig 49 Structural formulas of vitamins (*continued*)

Undernutrition

Definition As used here the term *under nutrition* means a state of nutritional defi ciency predominantly of calories and pro- tein There may or may not be a deficiency of other nutrients The term is not a for tunate one lacking specificity as to nutri ent and degree of nutritional deficiency Nevertheless the term has come to have rather wide acceptance as meaning calorie and protein deficiency disease primarily

Although it is customary to distinguish between calorie deficiency and protein de ficiency calorie deficiency disease is in effect protein deficiency Experimentally protein deficiency can be produced by feed ing either a protein-deficient diet or a diet inadequate in calories In the latter the calorie deficiency leads to the burning of protein for fuel (energy) and even though the amount of protein is adequate as such the protein is diverted to combustion and becomes insufficient for the body s needs as protein A deficiency of calories in the diet causes disease only when it causes too much body protein to be burned for energy This occurs only after the fat stores have been consumed or nearly consumed In a person of normal weight these stores will not be large and may be soon exhausted depending on the extent of calorie defi ciency In obese subjects the process is much longer (it is the basis of weight re duction) When fat is gone protein is next consumed Injury and deficiency disease may be said to exist when more than the small reserve of body protein has been burned Thus calorie deficiency disease becomes in effect protein deficiency disease In practice the deficiency is usually mixed from the beginning

Etiology Deficiencies of protein and cal ories result from an inadequate intake ab sorption and utilization of food and are common in many diseases ranging from the psychoneuroses to gastrointestinal ob struction Simple idiopathic starvation is only occasionally encountered

However deficiencies in the *intake* of protein and calories though common enough in disease and injury are not the only cause of actual protein deficiency dis ease or undernutrition Many kinds of in jury and disease are accompanied by a spontaneous idiopathic negative nitrogen balance This is occasioned by an excess urinary excretion of nitrogen apparently mediated by the action of adrenal cortical hormones This excess secretion of nitro gen is independent of intake which is often reduced in disease and injury and is ap parently the result of tissue breakdown In fact it may be impossible to match the excretion by increasing the intake i e to bring about nitrogen balance even when the intake is increased by artificial means to high levels This fact has led some per sons to conclude that the negative nitrogen balance is a beneficial or protective reac tion to injury despite the untoward effects it causes This is possibly true Neverthe less there are many examples of reaction to disease primarily beneficial which when excessive become harmful and re tard recovery

The phenomenon just described is some times spoken of as the *catabolic* phase of reaction to injury or disease It persists for a variable length of time and exists to a variable degree depending on a variety of factors Even so simple a restriction as confinement to bed may produce this effect The most striking and uncomplicated ex amples are seen in fractures of the long bones in previously healthy and well nour ished persons or in severe burns In these circumstances the negative nitrogen bal ance stands out as a sharply defined ab normality clearly related to the acute in jury and without any background of dis ease or other apparent cause

The reaction occurs in a variety of in juries and diseases in severe burns after major surgical operations especially those in which the peritoneum is opened with infections such as osteomyelitis empyema and abscesses and with some infectious diseases such as typhoid fever and menin gitis In addition to the original reaction similar though usually less severe reac tions may occur as the result of complica tions during the course of an illness The changing of casts secondary operations the opening of abscesses and the occur rence of secondary or complicating infec tions or infectious disease all may be ac companied by a return or exaggeration and prolongation of the nitrogen deficit and hence a delay in the onset of the anabolic or recovery phase

It is clear that in many instances the nitrogen deficit will be aggravated and increased by a diminished intake of pro teins and calories A number of factors are responsible for this diminished intake After injury and in many diseases there is often a loss of appetite and hence a lessened intake of food With this specific loss of appetite there are often the factors of unappetizing meals poorly prepared and served weakness difficulties of recum

VITAMIN | RELATED COFACTOR

Mio Inositol

Vitamin E
(α tocopherol)

$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$

Linolenic acid
(a polyunsaturated fatty acid)

FIG 49 Structural formulas of vitamins *(continued)*

It should be noted that for several of the vitamins some degree of biosynthetic capacity does exist within the human animal This may reside in the bacteria of the gastrointestinal tract as is probably the case with vitamin K or within the tissues of the mammal proper as is the case with choline The composition of the remainder of the diet may largely influence the nutritional need for certain vitamins Thus in the presence of a plethora of methionine symptoms of choline deficiency cannot be induced If the tryptophan content of the diet is high niacin can be synthesized at a rate compatible with survival and health Appropriate solar radiation results in the conversion of 7 dehydrocholesterol an abundant metabolic product in man into vitamin D_3 and circumvents the need for vitamin D in the diet

The nutritional requirements for all cells in the mammalian body are not identical Thus it is possible for one tissue to supply some ingredient which is essential for the proper functioning of another tissue Studies of the nutrients which must be supplied to certain tissue cultures derived from human material have revealed requirements not exhibited by intact man An example of such a requirement is that for glutamine exhibited by cultures of HeLa cells

In the absolute sense those coenzymes containing vitamin contributions are neither more nor less important than are a variety of other coenzymes which can be totally synthesized in the body Adenosine triphosphate which contains no vitamin residues is every bit as essential to normal cell function as is diphosphopyridine nucleotide One may speculate that of the many mutations entailing the loss of one or another enzymic activity certain ones are lethal and others are compatible with life and reproduction Among the lethal mutations are those involving loss of capacity to synthesize an essential tissue constituent not represented in the normal diet or required in a more continuous supply than is provided by three meals a day When a mutation results in loss of ability to synthesize an essential cell constituent which can be adequately supplied in the diet a new vitamin is born

DeWITT STETTEN JR

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concerned with enzymatic processes Body reserves protect in the case of those nutrients for which there is a large storage capacity—vitamin A for example Forced feeding to prevent or minimize the calorie and protein deficit will of course expose the patient to deficiencies of those vitamins such as the B complex concerned with metabolic oxidative mechanisms unless natural vitamin-carrying foods are supplied A good example of the need for supplement is parenteral feeding with glucose after operations

One important exception to the general lack of vitamin and mineral deficiencies in undernutrition should be made namely that relating to calcium In a variety of traumas excessive calcium excretion mainly urinary accompanies the excess secretion of nitrogen If it is continued and sufficiently severe there occurs an actual calcium deficiency represented by demineralization of the skeleton in varying degree sometimes sufficient to result in pathological fractures This loss like that of nitrogen can often be minimized but not always overcome by an increased intake of calcium There is the added complication of urinary calculi formed because of the high concentration of calcium in the urine combined in some cases with relative immobility (confinement to bed) There is insufficient evidence however that added calcium in reasonable amounts in the diet increases to any significant degree the likelihood of stone formation

Diagnosis The diagnosis of undernutrition is on the whole easy in fact the condition can in many instances be anticipated and prevented—true preventive medicine

A patient when seen by the physician *should have an appraisal of the state of* nutrition the probable effects of the disease on his nutrition and what is needed for the prevention or treatment of nutritional disease Often this will require only the usual history physical examination and routine laboratory work but special laboratory tests may be needed For the patient who is injured or acquires an illness while in a normal state of nutrition the need can be determined in general from the nature of the illness and its severity and probable duration but complications and variations in the response of the patient and his cooperation may require modification from time to time For instance in fractures of the large bones or severe trauma in serious burns and in most major surgical operations for acute diseases an immediate negative nitrogen balance and calorie deficit can be anticipated This should be met by nitrogen and calorie intakes to overcome or minimize these deficiencies

Weight is of course the earliest and at the same time simplest guide to undernutrition unless it is masked by edema Losses below 10 per cent of calculated ideal body weight may in general be considered evidence of actual protein deficiency However in some circumstances obese persons may have protein deficiency without calorie deficiency or reduction of weight below the ideal level Hypoproteinemia can be detected by determining the concentration of and total circulating plasma proteins Ordinarily the determination of the total serum proteins by the simple specific gravity methods suffices as a general diagnostic test and guide but the greater significance of the albumin fraction and the possibility that albumin is depressed while total proteins remain normal or near normal make it desirable to determine serum protein fractions when such a situation is suspected Accurate nitrogen balance studies are not often needed in these patients Edema except in patients with complicating renal or cardiac disease is nearly always related to the hypoproteinemia and is in itself a strong indication of protein deficiency It should indicate the need for a serum protein determination It must be emphasized that edema may mask actual loss of tissue Retention of 10 pounds of water can occur without visible edema

The diagnosis of other possible nutritional deficiencies is made in the usual manner Knowledge of the situation should lead one to anticipate such possible deficiencies and be on the watch for them

Treatment. In practice two stages of the reaction to injury or disease can be rather sharply differentiated and differ in their practical management The first is the initial period when only the metabolic disturbance is present and no nutritional deficiency disease has occurred In this stage there is the possibility of preventing or minimizing serious effects The second stage is that in which a greater or lesser deficiency has developed

The prevention and treatment of undernutrition are simple and easy in principle No difficult highly specialized or expensive techniques are necessary With occasional exceptions inexpensive materials may be used But they do require close attention and supervision on the part of the physician the nurse and other personnel as

bency and apparatus nausea vomiting and the mental changes of illness Unfortunately to these are often added indifference to nutritional problems on the part of the physician and nurse and even misconception and ignorance regarding the *proper diet and nutrient requirements* In some cases the nitrogen (protein) deficit is still further increased by loss of nitrogen from hemorrhage exudates transudates and discharge from wounds and burned surfaces from diarrhea and vomiting even from albuminuria when this is present

The catabolic phase just described is followed by an *anabolic* phase during which the nitrogen balance becomes positive (provided intake is adequate) nitrogen is retained and protein formed the tissues are restored and weight is regained It corresponds to the period of convalescence and recovery and is deficient or lacking in unfavorable circumstances

Morbid Anatomy and Physiology The effect of this negative nitrogen (and calorie) balance depends on its severity and duration and on the nutritional state of the patient As has already been stated it is ordinarily most severe in a previously healthy and well nourished person (for a given grade of injury) and curiously slight or absent in those already ill and poorly nourished as though the body lacked the ability to respond normally (and defensively?) to injury It should be remembered however that the latter group are already in a state comparable to the end stage of an initially well nourished group which has suffered from the full and severe effects of such a reaction The restorative if not the preventive *treatment is therefore the same* in both

The spontaneous result of the reaction represents a balance between the severity and duration of the reaction and the resistance (nutrition) of the patient If the process is mild and of short duration in a well nourished patient little harm is done Such would be the effect from a mild burn or minor fracture The body has a sufficient reserve of protein and calories (fat) to tide it over To say in such cases that nutritional deficiency disease is present would be incorrect However if the reaction is severe and prolonged is not limited by treatment and consumes the reserve resources of the body actual deficiency disease does occur Primarily it is a protein deficiency although other nutrients as will be shown later may be *involved*

Keys and his associates have well demonstrated experimentally the effects of this deficiency without the complications of accompanying disease They may be described as illustrating the basic harmful results of such a deficiency These may be aggravated or complicated by the effects of the primary injury or illness

The principal outward manifestation of this undernutrition is loss of body weight at first slight and representing mostly loss of fat When it is more severe and of longer duration there is a loss of tissue protein revealed externally by atrophy of muscles There is however a concomitant loss of native protein from parenchymatous organs and the blood plasma This is easily demonstrable by measurements of heart size and is also clearly evident in the liver and other parenchymatous organs There are accompanying physiological changes such as weakness hypothermia bradycardia and lowered basal metabolism together with significant mental changes of a character resembling those of the psychoneuroses With the hypoproteinemia there may be edema which if severe is not necessarily confined to the legs Decubital ulcers are a common complication

There is evidence also that more subtle changes of a harmful nature may accompany this undernutrition such as interference with immune body formation and hence with resistance to infection (a notorious complication of debility) and with production of secretions and enzymes Besides interference with such specific defenses against infection there may be secondary infection and impaired healing of wounds related to impaired health of tissues resulting from edema

In the presence of disease many of these abnormalities that are clearly evidenced in uncomplicated experimental undernutrition are aggravated or modified Fever and infection may prevent bradycardia and elevate the metabolism The weakened heart may be enlarged instead of smaller Edema may be massive *with effusions into the* serous sacs and weight may fail to decrease or may even increase because of the dropsy

So far little has been said of a deficiency of other nutrients such as vitamins and minerals Deficiencies of these are relatively uncommon in *the condition described here* particularly in those who were in good health and nutrition before the onset of the particular disease or injury The reduction in calorie consumption and slowing of metabolic processes accompanying many disease states themselves tend to reduce requirements *particularly of the vitamins*

red blood cells plasma fluid and electrolytes It is assumed in this discussion that such replacement of acute losses has been made Occasionally however intravenous feeding is necessary for the maintenance or restoration of nutrition For this purpose plasma or a solution of amino acids is used for nitrogen Glucose and an emulsion of fat supply fuel The recent availability for intravenous injection of emulsions of fat with their high caloric value makes it possible to maintain nitrogen equilibrium and caloric balance for relatively long periods It also lessens the need for large amounts of fluid which might overtax a weak heart cause circulatory failure induce or exaggerate edema and even provoke pulmonary edema and secondary pneumonia Electrolytes and supplements of other nutrients such as vitamins and minerals may be added as needed

There are drawbacks to intravenous feeding however The salt in solutions of amino acids may be undesirable Thrombosis of the veins used for injection occurs and may interfere with prolonged feeding Febrile reactions may occur The psychological influence of eating is lacking Therefore intravenous feeding particularly by itself should be used only after careful consideration of the need and suitability and for no longer than necessary Supplements of other nutrients such as vitamins and minerals should be given when necessary

Except perhaps in burned patients vitamins and minerals present little difficulty in previously healthy persons unless the illness is severe and prolonged and has resulted in severe undernutrition Adequate amounts for maintenance should be assured if these amounts are not available in the food they should be provided as supplements In particular provision should be made for adequate amounts of those vitamins directly concerned with cellular oxidations—thiamine riboflavin and niacin—when patients are maintained on large intakes of pure carbohydrates such as glucose that carry with them no complementary vitamins In parenteral administration somewhat larger doses of these vitamins should be given than are normally required because of greater excretion In previously ill patients or those seen for the first time with nutritional deficiency disease an appraisal should be made of their status in respect to vitamins and minerals and adequate restorative and maintenance treatment should be instituted

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Kwashiorkor

In infants and young children severe protein deficiency may produce the syndrome known as kwashiorkor In classic or pure cases the deficiency is one of protein alone and the intake of calories usually from starchy foods low in protein is adequate If a mild to moderate deficiency of calories exists with the protein deficiency the result may be marasmic kwashiorkor A severe deficiency of both calories and protein produces the well known classic marasmus or starvation which differs in many respects from kwashiorkor

Kwashiorkor was first described and is found to the greatest extent in undeveloped areas of the world mainly in the tropics and subtropics Since it was first reported from Africa the disease has been reported in Central and South America India China the Philippines Fiji Indonesia Malaya the Caribbean islands and in Hungary and Italy Under proper conditions however it can occur anywhere The disease is most prevalent in weanlings though it occurs in infants at breast presumably because of deficiencies in the mother s or nurse s milk In tropical countries the disease is associated with the intake of characteristic native carbohydrate foods such as cassava yams and sweet potatoes notably poor in protein Where cereals such as rice and wheat are used the disease is less prevalent and less severe Though it occurs in maize-eating areas there is no specific relation to the consumption of that cereal Improvement following the simple provision of a complete

well as the whole hearted cooperation of the patient Much help can be derived from the use of *standardized procedures or routines* particularly in a hospital However as always each patient will present an individual problem his requirements will differ as will his response and he will need individual attention Routines can provide only the basic framework of the procedure within which adjustments must be made for each patient Standardized regimens will indicate the amount and kind of food and route of administration They will not assure its consumption Finally it is to be remembered that too much food in early realimentation of the severely undernourished *may be harmful*

A number of excellent diets for this purpose have recently been published In general 3000 to 5000 calories and 120 to 150 gm of protein are necessary and advisable *in the types of injury and disease in which* possible undernutrition may develop Experience has shown that in many cases it is not necessary or desirable and may be harmful to secure complete nitrogen equilibrium during the early and more marked stage of the catabolic reaction the disadvantages and difficulties of attempting to supply huge amounts of protein outweighing the advantages However sufficient protein and calories should be administered to provide a high intake of nitrogen overcome the calorie deficit and take full advantage of the beginning of the anabolic period which will probably be *hastened* by this treatment

When possible this nourishment should be provided as ordinary food supplemented when necessary by special feedings In general *an attempt should be made to secure* an intake of around 2500 calories and 90 to 100 gm of protein by ordinary meals The additional requirements are met by supplements These are most satisfactorily furnished *as milk drinks composed of milk* with added skim milk powder or prepared casein and glucose A variety of satisfactory formulas have been devised A typical one provides 28 gm of protein and 343 calories for *each 240 ml Therefore three* such feedings will add 84 gm of protein and 1029 calories or a total of 160 to 180 gm of protein and 3500 calories if the regular meals are consumed

A careful record of intake—*calories and* nitrogen—should be maintained in such patients and it can be assumed that if intakes of around 3500 to 4000 calories and 120 to 150 gm of protein are secured the nitrogen deficit will *be abolished or* minimized in most cases Losses beyond about 10 per cent of calculated ideal body *weight should be avoided if losses* exceed this figure a more careful determination of the nitrogen balance should be made In burned patients particularly and in those with exudates draining sinuses dysentery and other causes of abnormal loss of protein a careful check of the probable balance must be made to determine the necessary intake which in some cases may be unusually large For instance it has been calculated that an average sized man with a third degree burn of 50 per cent of his body surface may lose as much as 19 9 gm of nitrogen in twenty four *hours from the burned surface equivalent* to 124 gm of protein

With patients who are already in a state of nutritional deficiency disease more strenuous treatment is necessary because the problem is one of replacement rather than prevention—the replacement of losses rather than maintenance of reserves Furthermore speed is highly desirable and delay merely prolongs recovery and convalescence Loss of weight and muscle atrophy with due consideration for edema are again the best general evidence of a state of deficient protein nutrition Hypoproteinemia indicates a cause of edema and gives a rough index of the degree of protein loss from other body tissues and organs Intakes graduated up to as high as 5000 to 6000 calories or higher and 200 to 300 gm of protein may be required and be very effective in severe deficiencies

In patients with nutritional disease already established and in some other circumstances the ordinary intake of food by *mouth may be inadequate* and tube or parenteral feeding may be necessary It may also be necessary in delirious or mentally ill patients in those with disease of the gastrointestinal tract especially as a *preoperative procedure when haste* is necessary or desirable and for those who do not cooperate by ingesting adequate amounts of food Often such feeding is best accomplished by stomach or duodenal *tube which can be used intermittently* or for a continuous drip For this purpose a variety of formulas for liquid foods are available most of them similar to those used for supplemental feeding by mouth *In some cases it may* be necessary to use intravenous feeding alone or in combination with gastric or duodenal gavage Ordinarily such intravenous feeding is only for replacement of nutrients lost acutely such *as in operations* or trauma and includes

imbalance added potassium chloride is sufficient and may be given with the formula In moderate and severe cases with marked dehydration buffered hypotonic solutions such as the Ringer lactate solution of Hartman may be given intravenously in doses of 40 to 50 ml per kg Later Dennis solution may be given more slowly Vomiting may alter the picture by the loss of hydrochloric acid Close clinical observation as well as laboratory facilities to the extent available are necessary to combat complex derangements

Other deficiencies as for example pellagra beriberi and vitamin A deficiency should be treated adequately In the marasmic form total calories must be adequate Because susceptibility to infection is so great routine antimicrobial therapy is recommended

JOHN B YOUMANS

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Vitamin A Deficiency

Vitamin A is an unsaturated cyclic alcohol soluble in fat solvents

As far as is known the original source for all the vitamin A in all species of fish birds and mammals is the carotenes and related carotenoids Vitamin A occurs in the animal kingdom and is present chiefly in the liver although the kidney lungs and fat droplets may contain some For many years vitamin A_1 has been known to occur in sea fish oils and more recently vitamin A has been found in the oils of certain fresh water fish The provitamins A are not ordinarily found in large quantities in the healthy person since they are transformed into vitamin A and utilized in that form A low plasma vitamin A and a high plasma carotene content suggest a failure in liver function

One of the chief functions of vitamin A in the body is the maintenance of epithelial tissues In the absence of vitamin A over a sufficient period of time the cells atrophy and some of the basal cells proliferate This produces a picture of keratinized epithelium This type of epithelium is susceptible to bacterial invasion In the late stages severe infections of the eye respiratory organs genitourinary tract and mouth are likely to occur Another function of vitamin A is its participation in the so called "visual cycle" After prolonged deprivation of vitamin A impairment of vision may occur giving rise to a form of night blindness Wolbach has brilliantly demonstrated that the skeletal growth of young rats is retarded by vitamin A deficiency He showed that mechanical damage of the brain and spinal cord results from the continual growth of the central nervous system within its skeletal framework

A deficiency of vitamin A can sometimes be detected by dark adaptation tests or by an examination of scrapings from the eye or from the vagina There is no absolute correlation between the vitamin A content of the blood and biophotometer readings or examination of the scrapings from the epithelial surfaces or the general physical examination The first symptom referable to the eyes is loss of visual acuity in dim light This symptom occurs in various diseases affecting the eye and is not pathognomonic It should be seriously considered however in a person whose diet has been deficient in vitamin A or in a patient who has cirrhosis of the liver any generalized alimentary tract disease or nutritive failure In the late stages the ocular disease is termed *xerophthalmia* Prolonged mild deficiencies of vitamin A may lead to the development of Bitot spots gray triangular patches in the scleral conjunctiva produced by an accumulation of epithelial cells These spots do not occur over the cornea and they do not ulcerate

Within the past few years cutaneous lesions caused by a deficiency of vitamin A have been described The earliest clinical skin change is simple dryness The most characteristic skin lesions are the plugs which form in the hair follicles resulting in a rough dry skin known as hyperkeratosis (see Fig 50) Follicular hyperkeratosis occurs typically on the extensor surfaces of the arms and thighs and tends in some ways to resemble so-called "goose flesh in its appearance

Treatment Green leafy vegetables all yellow vegetables and fruits supply provitamin A in the human diet Vitamin A proper

protein in the diet (or amino acids) indicates protein deficiency as its cause

In the classic sugar baby form the infant fails to grow becomes at first irritable then apathetic anorectic and listless but irritable when aroused Edema develops first localized to feet and legs and in severe cases becomes anasarca Subcutaneous fat is often well retained

In marasmic kwashiorkor there is severe tissue wasting loss of subcutaneous fat and usually dehydration Fluid and electrolyte balance are disturbed to a degree and kind not seen in the wet or classic form In both the classic and marasmic forms there are disturbances in enzyme activity which are not present in simple marasmus

In children of the pigmented races particularly changes occur in the skin and hair which are characteristic though not universal They vary greatly in different areas and with different forms and degrees of severity of the disease In Negroes the skin and hair may take on a reddish cast which is one suggested explanation for the use of the name kwashiorkor one meaning of which is "red The hair is often bleached dry and sparse In very acute cases these changes may not appear In the hair the dyspigmentation may be noted as a band or zone in children who have had the disease and recovered The skin in addition to dyspigmentation may appear pale and may exhibit darkened thickened patches on limbs and back which may desquamate leaving pink almost raw surfaces of a pellagroid appearance There may be generalized desquamation

As is nearly always true in nutritional deficiency disease other deficiencies are apt to complicate the picture Furthermore parasitic infestation and diseases such as malaria may coexist adding to the severity of the illness as well as confusing the clinical appearance They may also precipitate the appearance of the disease in borderline states of deficiency

Kwashiorkor resembles pellagra and has been confused with it Pellagra undoubtedly occurs with kwashiorkor but kwashiorkor occurs independently and is not a form of pellagra Coexisting beriberi vitamin A deficiency and tropical anemia have been observed

The most common abnormalities disclosed by laboratory tests are hypoproteinemia and electrolyte and fluid imbalance The most frequent and serious pathological change is a fatty liver The hypoproteinemia is characteristic and an almost constant feature It is essentially a hypoalbuminemia with the globulins usually elevated the gamma globulins almost exclusively Blood urea is reduced as is total cholesterol Alkaline phosphatase cholinesterase amylase lipase and trypsin are reduced Anemia is not a characteristic of the disease itself but may be present from other causes

Fluid and electrolyte imbalance do not occur in the pure form In the marasmic type dehydration is common and is customarily associated with diarrhea In this situation the fluid imbalance is no different from that seen in other diarrheal disease However protein deficiency alone can produce a deficiency of potassium and an imbalance of other electrolytes with a concomitant shift in compartmental fluids

The pathological changes occur mainly in the liver though other changes such as atrophy of intrinsic and extrinsic musculature and of the heart as is found in marasmus would be expected The liver is nearly always involved usually enlarged with fatty infiltration cellular necrosis and fibrosis singly or in combination Fat may be present up to 30 per cent In late and severe cases the liver may be shrunken soft and excessively fatty The frequency of infantile (as well as adult) hepatic cirrhosis in regions where kwashiorkor is prevalent suggests a possible relation to the processes occurring in kwashiorkor Obviously other possible causes of cirrhosis such as infectious hepatitis exist

The mortality in severe forms of kwashiorkor is high up to 80 per cent With recognition of the nature of the disease the detection of early and mild cases and the excellent response to treatment if it can be provided the mortality should be less Treatment consists primarily of the administration of protein This is best given as milk but other proteins (soybean for example) can be employed Such treatment will be effective in most cases if irreversible changes have not taken place In those parts of the world in which the disease is most common local habits and customs may interfere with proper treatment Feeding may present great difficulties and infants may refuse to take other than their accustomed food However supplements can be provided in many ways When possible tube feeding may be employed and solutions of amino acids have been used with success Blood and plasma transfusions have been employed but are principally a temporary aid When electrolyte and water imbalances are present they should be corrected With mild electrolyte

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As far as is known the original source for all the vitamin A in all species of fish birds and mammals is the carotenes and related carotenoids Vitamin A occurs in the animal kingdom and is present chiefly in the liver although the kidney lungs and fat droplets may contain some For many years vitamin A_1 has been known to occur in sea fish oils and more recently vitamin A has been found in the oils of certain fresh water fish The provitamins A are not ordinarily found in large quantities in the healthy person since they are trans formed into vitamin A and utilized in that form A low plasma vitamin A and a high plasma carotene content suggest a failure in liver function

One of the chief functions of vitamin A in the body is the maintenance of epithelial tissues In the absence of vitamin A over a sufficient period of time the cells atrophy and some of the basal cells proliferate This produces a picture of keratinized epithelium This type of epithelium is sus ceptible to bacterial invasion In the late stages severe infections of the eye respira tory organs genitourinary tract and mouth are likely to occur Another function of vitamin A is its participation in the so called "visual cycle" After prolonged de privation of vitamin A impairment of vision may occur giving rise to a form of night blindness Wolbach has brilliantly demonstrated that the skeletal growth of young rats is retarded by vitamin A defi ciency He showed that mechanical damage of the brain and spinal cord results from the continual growth of the central nervous system within its skeletal framework

A deficiency of vitamin A can sometimes be detected by dark adaptation tests or by an examination of scrapings from the eye or from the vagina There is no absolute correlation between the vitamin A content of the blood and biophotometer readings or examination of the scrapings from the epithelial surfaces or the general physical examination The first symptom referable to the eyes is loss of visual acuity in dim light This symptom occurs in various dis eases affecting the eye and is not pathogno monic It should be seriously considered however in a person whose diet has been deficient in vitamin A or in a patient who has cirrhosis of the liver any generalized alimentary tract disease or nutritive fail ure In the late stages the ocular disease is termed *xerophthalmia* Prolonged mild deficiencies of vitamin A may lead to the development of Bitot spots gray triangular patches in the scleral conjunctiva produced by an accumulation of epithelial cells These spots do not occur over the cornea and they do not ulcerate

Within the past few years cutaneous lesions caused by a deficiency of vitamin A have been described The earliest clinical skin change is simple dryness The most characteristic skin lesions are the plugs which form in the hair follicles resulting in a rough dry skin known as hyperkera tosis (see Fig 50) Follicular hyperkera tosis occurs typically on the extensor sur faces of the arms and thighs and tends in some ways to resemble so-called "goose flesh" in its appearance

Treatment Green leafy vegetables all yellow vegetables and fruits supply provita min A in the human diet Vitamin A proper



FIG 50 Follicular hyperkeratosis of vitamin A deficiency





FIG 51 Hemorrhagic jaundice of vitamin K deficiency

FIG 52 Rickets due to vitamin D deficiency



FIG 53 Pitting edema of legs ("wet beriberi") and peripheral neuritis of vitamin B deficiency

Table 4 Food and Nutrition Board National Research Council Recommended Daily Dietary Allowance Revised 1958

DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE U S A

(Allowances are intended for persons normally active in a temperate climate)

	AGE YEARS	WEIGHT KG (LB)	HEIGHT CM (IN)	CALORIES	PROTEIN GM	CALCIUM GM	IRON MG	VITAMIN A IU	THIAM MG	RIBO MG	NIACIN[2] MG EQUIV	ASC ACID MG	VITAMIN D IU
Men	25	70 (154)	175 (69)	3200[3]	70	0.8	10	5000	1.6	1.8	21	75	
	45	70 (154)	175 (69)	3000	70	0.8	10	5000	1.5	1.8	0	75	
	65	70 (154)	175 (69)	2550	70	0.8	10	5000	1.3	1.8	18	75	
Women	25	58 (128)	163 (64)	2300	58	0.8	12	5000	1.2	1.5	17	70	
	45	58 (128)	163 (64)	2200	58	0.8	12	5000	1.1	1.5	17	70	
	65	58 (128)	163 (64)	1800	58	0.8	12	5000	1.0	1.5	17	70	
	Pregnant (second half)			+300	+20	1.5	15	6000	1.3	2.0	+3	100	400
	Lactating (850 ml daily)			+1000	+40	2.0	15	8000	1.7	2.5	+2	150	400
Infants[4]	0 1/12[4]				See Footnote 4								
	2/12 6/12	6 (13)	60 (24)	kg × 110		0.6	5	1500	0.4	0.5	6	30	400
	7/12–12/12	9 (20)	70 (28)	kg × 100		0.8	7	1500	0.5	0.8	7	30	400
Children	1–3	12 (27)	87 (34)	1300	40	1.0	7	2000	0.7	1.0	8	35	400
	4–6	18 (40)	109 (43)	1700	50	1.0	8	2500	0.9	1.3	11	50	400
	7 9	27 (60)	129 (51)	2100	60	1.0	10	3500	1.1	1.5	14	60	400
	10–12	36 (79)	144 (57)	2500	70	1.2	12	4500	1.3	1.8	17	75	400
Boys	13 15	49 (108)	163 (64)	3100	85	1.4	15	5000	1.6	2.1	21	90	400
	16–19	63 (139)	175 (69)	3600	100	1.4	15	5000	1.8	2.5	25	100	400
Girls	13 15	49 (108)	160 (63)	2600	80	1.3	15	5000	1.3	2.0	17	80	400
	16–19	54 (120)	162 (64)	2400	75	1.3	15	5000	1.2	1.9	16	80	400

[1] The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. The recommended allowances can be attained with a variety of common foods providing other nutrients for which human requirements have been less well defined.

[2] Niacin equivalents include dietary sources of the preformed vitamin and the precursor tryptophan. 60 milligrams tryptophan equals 1 milligram niacin.

[3] Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity and environmental temperature.

[4] The Board recognizes that human milk is the natural food for infants and feels that breast feeding is the best and desired procedure for meeting nutrient requirements in the first months of life. No allowances are stated for the first month of life. Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis due to different rates of maturation of digestive, excretory and endocrine functions. Recommendations as listed pertain to nutrient intake as afforded by cows' milk formulas and supplementary foods given the infant when breast feeding is terminated. Allowances are not given for protein during infancy.

is supplied by milk liver and to a lesser extent by kidneys and animal fats A liberal supply of these foods in the diet is excellent prophylactic therapy Persons with night blindness xerophthalmia or keratomalacia can usually be relieved by ingestion of 5000 to 50 000 units of vitamin A daily in the form of synthetic vitamin A a potent fish liver oil or carotene The skin lesions may require doses of 50 000 units of vitamin A daily They respond slowly as a rule three to four months of therapy elapse before beneficial results are observed Carotene which is a precursor of vitamin A can be given in such large amounts that it causes a yellowish discoloration of the skin which often is confused with jaundice

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Vitamin B Deficiencies

BERIBERI

Definition Beriberi is a clinical syndrome associated etiologically with a faulty food supply or an alteration of metabolism associated with thiamine deficiency It is characterized clinically by multiple neuritis serous effusions edema muscular atrophy and cardiovascular changes It occurs sporadically and endemically and passes in great waves over the Oriental countries The disease is associated with ignorance and poverty and may appear in any race and at any age

History Though the precise origin of the word beriberi is unknown the term undoubtedly arose from an Oriental language many centuries ago There is good reason to believe that the disease was described in the Niching (2697 B C) In 1642 Jacobus Bontius the first Occidental physician to describe the disease pointed out that the natives of Java called it beriberi During the nineteenth and twentieth centuries great interest arose in the recognition and prevention of beriberi and closely related diseases During this period of renewed clinical interest investigators applied dietary methods of prevention to special groups of the population with great success

Incidence Beriberi occurs sporadically throughout the world It is prevalent both among infants and adults in the endemic areas of China Japan *Indonesia Brazil* India the Malay Peninsula and the Philippine Islands At times sudden outbreaks of the disease occur in these countries and in prisons and asylums of the Western World

Recent studies show that beriberi (nutritional peripheral neuritis) is much more prevalent in the Western Hemisphere than is commonly supposed Its incidence is high among pellagrins alcohol addicts and pregnant women It is frequently associated with organic disease and often coexists with other nutritional deficiencies

Etiology The results of clinical and experimental studies point to a definite relationship between an unbalanced diet abundant in decorticated cereals and the development of beriberi Such diets are known to be deficient in thiamine (Vitamin B_1) The ingestion of excessive amounts of fish or molluscs sometimes causes foxes to develop a type of thiamine deficiency The enzyme thiaminase in the fish some way inactivates the thiamine so that symptoms may appear As far as we have been able to learn this mechanism has not produced a case of beriberi in man Although it has not been proved that one specific factor is the sole cause of the disease clinical and experimental studies leave no doubt that persons with beriberi are greatly benefited by vitamin B_1 therapy

It appears that man cannot synthesize thiamine nor can he store it to any great extent The length of time or the degree to which a deficiency must be present before clinical evidence of the disease appears is not known Clinical studies show that the depletion period is extremely variable ranging from a few weeks to months or years They show also that certain factors predispose to and precipitate the development of the disease Prominent among these are increased physical exercise fevers hyperthyroidism and other conditions which are accompanied by an increased metabolic rate pregnancy and lactation digestive disturbances and chronic debilitating diseases which cause improper ingestion assimilation or utilization of food

At the present time the precise manner in which a deficiency of thiamine operates

to produce the symptoms of beriberi is not understood Cocarboxylase (thiamine pyro phosphate) has antineuritic properties and plays a prominent role in oxidation and reduction

There is considerable evidence that other nutritional diseases often coexist with beri beri Persons with beriberi frequently have a deficiency of nicotinic acid and riboflavin

Morbid Anatomy Postmortem examina tions are of little value in making a diag nosis or in explaining the pathological physiology of the disease The findings are not constant but the process in general is one of degeneration affecting especially the myocardium the gastrointestinal tract and the nervous system The most common gross findings are emaciation of the body and atrophy of the muscles particularly in the legs The body is often edematous the heart is dilated and hypertrophied and serous effusions and chronic passive con gestion of the viscera are commonly ob served Microscopic studies show diffuse edema in various tissues and degeneration of the involved nerves muscles and myo cardium Degeneration of the nerves varies from slight alteration to complete degen eration of the myelin and axis cylinder The affected muscles show a diffuse paren chymatous degeneration with loss of stria tions and hyaline and fatty changes The cardiac muscle fibers are often fragmented and contain hyaline and fatty material Postmortem findings in infants dying of beriberi are practically identical with those found in the adult The degenerative changes in the nerves are however less striking in the infant

Symptoms Beriberi may be an acute or chronic disease In the infant it is nearly always acute in the adult it is nearly al ways chronic The symptoms of infantile beriberi appear identical with those of the fulminating type in the adult Infantile beri beri is characterized by a rapid onset with diminished urinary secretion constipation rigidity of the body and cyanosis The child has a peculiar whine and cries most of the time He is weak has a rapid irregular pulse edema of the legs and usually dies suddenly or is rapidly and completely cured by treatment

In contrast the onset in the adult is usu ally insidious and the prodromata are vague and general Lassitude general itching dys pepsia tachycardia fatigue on exertion and tenderness of the muscles occur early After a variable period of time the symp toms can be associated with degeneration of the nervous system alteration of the gastrointestinal tract the presence of edema and serous effusions or enlarge ment and dilatation of the heart When the disease affects chiefly the peripheral nerves it is commonly called the dry type when it is especially characterized by acute car diac symptoms it is known as the "fulmi nating type and when it is associated primarily with edema and serous effusions it is referred to as the "wet type (Fig 53) Beriberi strikingly selects the vagi the pe ripheral nerves of the extremities and the vasomotor system

Not all symptoms are necessarily pres ent in a given patient and the order of their appearance may vary A patient with predominating cardiac symptoms may sud denly exhibit gastrointestinal symptoms such as a distaste for food vomiting or diarrhea the patient with gastrointestinal distress may suddenly display such myo cardial symptoms as dyspnea precordial pain and circulatory failure Either or both of the foregoing types may have or may develop peripheral neuritis conversely a patient with peripheral neuritis may have cardiorespiratory or gastrointestinal symp toms Serous effusions and edema may pre cede accompany or follow the cardiac gastrointestinal or nervous symptoms

The symptoms subside slowly in the adults who recover many months may pass before there is a restoration of function if indeed complete restoration ever does take place Often after the active phase of the disease disappears residual paralysis mus cular atrophy and cardiac enlargement re main for a long time

Nervous Symptoms The chronic cases have involvement of the nervous system The early course is characterized by ting ling of the hands and feet and by weak ness of the legs The clinical manifestations are caused by an ascending symmetrical peripheral neuritis The deep reflexes of the extremities at first increase later dimin ish and finally are absent Tenderness in the calf muscles and sharply defined patches of anesthesia and numbness often appear early This process affects particu larly the extremities and sometimes the diaphragm producing wasting of the muscles contractures ataxia lack of co ordination and dyspnea Sensations of touch pain and temperature are usually decreased but at times may be increased Anxiety states and mental confusion are common manifestations

Cardiorespiratory Symptoms When the disease is characterized especially by car diac symptoms (fulminating type) the



FIG 54 Muscular atrophy of the upper extremities in a beriberi patient with severe peripheral neuritis *Compare the wasting of all muscle groups in the arms with fairly normal muscles of the shoulder girdle and neck*

adult patient usually dies suddenly and without a history of prodromal symptoms Ocasionally however a person with gastro intestinal and neurological symptoms suddenly suffers the fulminating type of the disease The cardiac symptoms are always striking The most common ones are palpitation tachycardia dyspnea lowered blood pressure cardiac murmurs changes in the electrocardiogram and paralysis of the diaphragm associated with "high output failure Before death there is nearly always cardiac enlargement and dilatation pulmonary congestion edema cyanosis and vasomotor collapse

Digestive Symptoms Frequently there is nausea vomiting and epigastric distress These symptoms are especially prominent in the acute fulminating type and are often found with cardiac decompensation

Other Symptoms Edema is the most striking feature in many cases It usually begins in the legs and may progress until the whole body becomes involved Sometimes a typical case with the body bloated from anasarca appears emaciated after diuresis Hydropericardium and effusions into various serous cavities are common and a low serum protein can be demonstrated frequently At times the organs of taste smell hearing and sight are involved Libido decreases Anemia may appear in the later stages of the disease

Diagnosis The typical case can be readily diagnosed by means of a reliable dietary history and by the presence of certain characteristic physical findings Almost without exception the history reveals that adults who have beriberi have subsisted on a monotonous diet abundant in carbohydrates (chiefly milled rice wheat or corn) The physical findings are an enlarged heart peripheral neuritis edema and tenderness and atrophy of the muscles Infants who are restricted to the milk of women with beriberi usually acquire the disease during the first three months of life The diagnosis is made on the following objective findings constipation diminution in the volume of urine rigidity of the body irritability a rapid and irregular pulse weakness edema cyanosis and a peculiar whine

Though the atypical or mild cases occurring in infancy or later are probably more common than the typical ones the manifestations in such cases vary greatly and the disease is not easily recognized Since there is no specific laboratory test for beriberi it is often necessary to exclude the possibility of various types of heart disease diphtheria nephritis tabes alcoholism lead and arsenic poisoning pellagra scurvy and sprue before a positive diagnosis of beriberi can be made

Prognosis No disease requires more conservatism in making a favorable prognosis than does beriberi for a patient who seems to be recovering may suddenly exhibit cardiac symptoms and die The mortality rate is variable being around 5 per cent in the mild cases and reaching well over 50 per cent in the more severe ones The ultimate prognosis is dependent upon the age and general condition of the patient and upon the severity and duration of the disease In general patients with acute cardiac symptoms are least likely to survive If the adult is left untreated eventually incapacitation or even death is to be expected If however the disease is recognized and treated early the outlook is good provided the patient can and will follow recommendations Recovery is rapid and complete in infants who are given early and persistent treatment

Treatment Crystalline vitamin B_1 (thia

mine hydrochloride) is recommended for every case in which the diagnosis of beri beri is established It may be administered intravenously intramuscularly or orally Parenteral administration is recommended in severely ill cases especially when thiamine deficiency is associated with severe gastroenteric disturbances or with cardiac failure In such cases 30 to 50 mg should be given intravenously in sterile physiological saline twice daily For the average cases the parenteral administration of 10 mg twice daily is adequate Oral administration of 5 to 10 mg twice daily is sufficient for the mild case Brewers yeast wheat germ and tikitiki (an alcoholic extract of rice polishings) are effective therapeutic agents in the average case of thiamine deficiency The usual dose of brewers yeast and wheat germ is 6 ounces and of tikitiki 3 ounces The yeast and wheat germ are best tolerated if given in iced milk or eggnog at frequent intervals All persons who have a thiamine deficiency should be given a well balanced high caloric diet including foods rich in vitamin B_1 These foods are whole grain bread and cereals legumes lean pork liver heart kidney and milk All patients whether the disease is mild or severe should be kept at complete rest until convalescence is well established

For infants with beriberi the parenteral administration of 5 to 10 mg of crystalline vitamin B_1 is recommended After convalescence is established the same amount may be administered orally If crystalline vitamin B_1 cannot be procured an alcoholic extract of 100 gm of rice polishings (tikitiki) may be given daily If the child s mother has latent or manifest beriberi cow s milk should replace breast milk

Prevention Prevention in the adult or infant is dependent upon the ingestion assimilation and utilization of sufficient quantities of a well balanced diet The most logical means of ending beriberi as a world problem in the near future would be to pass and enforce a law preventing the overmilling of rice wheat and corn Grain products have long been the principal component of the poor man s diet Overmilling of the cereals has deprived the finished product of much of its natural mineral and vitamin content Consequently the foods which may constitute the major part of the diet of persons most in need of improvement in their nutritional status are nutritionally inferior The enrichment of flour and bread in this country is a step forward in improving the diets of these persons Until such time as proper diets are available to all people or until a law prohibiting the sale of overmilled cereals is passed and enforced the incidence of beriberi can be greatly decreased by the application of the following recommendations

1 Whole grain or enriched flour and bread should be substituted for the highly milled products

2 Foods must not be overcooked since excessive heat destroys vitamin B_1 The common habit of adding soda during the cooking process is detrimental and should be discontinued Foods should be cooked in as little water as possible and the water in which they are cooked should be used in soups or broths rather than discarded

3 Lean meat milk eggs fresh vegetables dried vegetables and nuts should make up at least 50 per cent of the daily diet

4 Any one of the following relatively inexpensive supplements is helpful in preventing beriberi and should be added to the daily diet whenever possible dried brewers yeast (1 ounce) wheat germ (2 ounces) or tikitiki (1 ounce) Infants are given indirect protection by preventing the disease in mothers and can be given additional protection by supplementing their daily diet with an alcoholic extract of 40 gm of rice polishings (tikitiki)

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PELLAGRA

Definition Pellagra is a noncontagious nonhereditary clinical syndrome affecting the skin alimentary tract and nervous system It is characterized by seasonal recurrences and relapses may occur in any race and at any age and is associated with deficiency in niacin and other factors in nutrition

History The term pellagra " from the Italian "pelle agra " meaning rough skin was first used in

medical literature in 1771 by the Italian physician Frapolli who found the word in common use among the peasant population of Lombardy The authentic history of the disease begins somewhat earlier in northern Spain In 1735 Gaspar Casal physician to King Philip V recorded his observations on mal de la rosa a malady prevalent among the peasantry in the province of Asturias Twenty years later Antonio Pujati reported its presence in northern Italy and in 1784 a special hospital for the treatment of pellagrins was established at Legano by warrant of Joseph II of Austria During the nineteenth century the disease was observed in many other countries chiefly in France Egypt and Rumania In the United States sporadic cases had been reported as early as 1864 from New York and Massachusetts but it was not until 1907 when Searcy called attention to the presence of a large number of cases of endemic pellagra in an asylum in Alabama that the seriousness of the situation in the southern part of the United States was appreciated Within the next few years many cases were reported from practically all southern and from many northern States

Incidence Pellagra formerly was prevalent in many countries The incidence was high in Egypt the United States Rumania Serbia Bulgaria Russia Italy and Spain Wilson stated that 30 per cent of the population of Egypt was affected with pellagra and the United States Public Health Service estimated that there were 400 000 cases annually in the United States It was believed that at least 10 per cent of the inmates of the insane asylums in the southern part of the United States were admitted because of pellagra Owing to the use of nicotinic acid pellagra has virtually been eradicated from the United States and greatly decreased in other countries

Etiology For many years opinion in regard to the cause of pellagra was divided At the present time the opinion is accepted that pellagra is a clinical syndrome caused primarily by a nutritional deficiency which may arise in one or more of the following ways (1) The person s diet may be inadequate in the antipellagric foods (2) His absorption may be impaired because of altered gastrointestinal function (3) His requirement for the antipellagric substances may be in excess of the amount supplied by a liberal well balanced diet

Goldberger advanced the theory that the pellagra preventive factor is a single substance vitamin B (G) the thermostable portion of the vitamin B complex and until recently many students of nutrition accepted this theory It is now known that what he termed vitamin B is not a single substance for it is composed of a number of active principles Four of the most important are niacin pantothenic acid pyridoxine and riboflavin It has been shown that niacin is a specific curative agent for the mucous membrane lesions for many of the symptoms arising from the alimentary tract and for the mental symptoms of human pellagra and that it aids in preventing recurrences of these symptoms Its relationship to the dermatitis of pellagra has been fully established After the administration of nicotinic acid the concentration of coenzymes I and II in the blood and urine of pellagrins is increased from subnormal to normal values The increase in concentration of these coenzymes which are fundamental to cell respiration parallels the clinical improvement of the patient Recent work has shown that tryptophan when given in large amounts promotes relief of symptoms in pellagrins

Certain predisposing and precipitating factors often play a role in the pathogenesis of the disease Important among these are fatigue insomnia loss of teeth infections food idiosyncrasies chronic alcoholism and diseases which cause improper ingestion assimilation or utilization of food Failure to consider all these conditions as underlying factors in the cause of pellagra has led to the designation of certain cases as "pseudopellagra pellagra sine pellagra postalcoholic dermatitis alcoholic pellagra and "secondary pellagra Such terms are confusing and should be abandoned the disease is or is not pellagra

From 1937 to 1945 we studied over 10 000 pellagrins who ingested inadequate diets We learned that pellagra usually coexists with beriberi riboflavin deficiency and other dietary deficiencies The diagnosis of pellagra therefore necessitates a thorough search for evidence of other deficiency syndromes and the institution of therapy specific *for each deficiency*

Morbid Anatomy The most common gross findings are generalized emaciation of the body and atrophy of various organs Pellagra can be diagnosed at the postmortem table only when the characteristic oral and skin lesions persist In some cases the walls of the gastrointestinal tract may show swelling reddening and ulceration of any portion in other cases the walls may be thin and atrophic The liver occasionally contains abnormal amounts of fat Histologically the skin lesions vary from atrophy to an intensive inflammatory reaction Similarly the microscopic picture of the intestinal lesions varies from *atrophy to* acute inflammation characterized by fibrin formation and collections of inflammatory cells When changes in the nervous system are demonstrable they are characterized by irregular areas of degeneration often in

volving the posterior and lateral columns of the spinal cord the posterior spinal ganglia and the Betz and Purkinje cells

Symptoms These arise chiefly from the skin gastrointestinal tract and nervous system *They vary greatly with each patient* arising in some from only one of the systems and in others from two or more

Prodromal Symptoms The onset of pellagra is often so gradual that the earliest symptoms may not be noticed by the patient Early in the disease there is a loss of strength particularly in the legs a change in appetite and usually though not always a decrease in body weight There may be also a change in mood or personality Pellagra in the early stages of the disease is often incorrectly diagnosed as neurasthenia

Skin Pellagrous dermatitis is not always present but when observed may be readily diagnosed by its appearance symmetry location and course Symmetrical lesions may appear on any part of the body but are most common over sites of irritation such as the hands wrists elbows neck under the breasts knees feet and in the perineal region A sharp line of demarcation at the periphery of the lesion separates the affected area from the healthy skin In the majority of cases pellagrous dermatitis is restricted to the exposed parts of the body and the dermal lesions of pellagra often appear after exposure to sunlight The dermatitis begins as an erythema resembling sunburn As the disease progresses the area becomes reddish brown roughened scaly and keratotic vesicles and bullae may form Desquamation usually begins at the center of the lesion and the underlying skin appears red and thickened *The intensity of the pigmentation* and the thickening of the skin tend to increase with each recurrence of the disease after repeated recurrences the skin may become either permanently pigmented thick and roughened or thin and atrophic (see Figs 58 59 60 61)

Alimentary Tract Both glossitis and stomatitis are early and common symptoms and are usually such as to be diagnostic of the disease In the beginning only the tip and lateral margins of the tongue are swollen and reddened (Fig 57) If treatment is not given the swelling increases the red discoloration becomes more intense and deeply penetrating ulcers may appear along the sides and tip—rarely on top Frequently a thick gray membrane filled with debris and Vincent s organisms covers the surface The tongue is usually hypesthetic though it may be hypersensitive The buccal membranes the mucocutaneous surface of the lips the gums and the palate may likewise be affected The course of the stomatitis is similar to that of the glossitis A burning sensation of the tongue and of the mucous membranes of the pharynx esophagus and stomach is not uncommon this is often aggravated by hot or acid foods Ptyalism nausea and vomiting may occur early but as a rule these are advanced symptoms of the disease About 50 per cent of pellagrins have no free hydrochloric acid even after histamine stimulation rennin and pepsinogen are likewise absent This achylia gastrica tends to persist during remissions The stools may be hard soft or watery but the odor is invariably foul Contrary to what is generally taught the bowels in the majority of mild cases act normally or are constipated Severe persistent diarrhea with several watery stools each hour tends to appear only in the more acute cases Abdominal distention discomfort and pain may be present at any time during the course of the disease but are more severe after a large meal

Nervous System Nervous symptoms are common but at the onset of the disease are often vague and ill defined The patient may complain of nervousness insomnia headaches dizziness muscular weakness and a bilateral burning of the hands feet and other parts of the body The tendon reflexes are frequently altered At first they may be exaggerated later decreased finally they may be absent The extremities particularly the legs may "feel numb or become paralyzed Typical subacute combined degeneration of the spinal cord with spasticity and ataxia is found Tremor and a spastic or ataxic gait are often associated with peripheral neuritis in the advanced cases

Mental Changes Pellagrins are subject to periods of depression and apprehension and unless treatment is administered hallucinations confusion delirium and complete disorientation may develop Tremor jerky movements and rigidity of the body frequently accompany these mental symptoms If such cases are given early and intensive treatment the mental symptoms seldom persist but in the absence of treatment the patient is likely to become psychotic

Organs of Special Sense Any of the organs of special sense may be affected loss of taste and smell is common

Genitourinary System Burning on urina



Fig 55 Photophobia epiphora and scleral injection in riboflavin deficiency



Fig 56 Cheilitis and photophobia in riboflavin deficiency



Fig 57 Glossitis of nicotinic acid deficiency



Fig 58 Pellagrous dermatitis of nicotinic acid deficiency



Fig 59 Pellagrous dermatitis of hands in nicotinic acid deficiency



FIG 60 Symmetrical exfoliating lesions on elbows and dorsal surface of the hands of a pellagrin in relapse Multiple areas of ulceration and a few large bullae can be seen

tion occurs frequently Libido is often decreased sterility is unlikely In the female acute pellagrous vaginitis with Vincent's infection is a usual finding Menstruation may be scanty or absent

Circulatory System In the mild case a slightly subnormal blood pressure is often noted In the severe case there is an increased pulse rate lowered blood pressure and vasomotor collapse Syncope and sudden death frequently occur

Blood The hemoglobin is less than 70 per cent in the majority of patients with severe pellagra The anemia is either macrocytic or microcytic in type

Temperature The temperature of the mild uncomplicated case is usually normal an elevation of several degrees is serious since it denotes the presence of an infection or a severe type of the disease

Diagnosis The typical case is easily diagnosed on the basis of a reliable history and careful physical examination The history is usually one of an inadequate or unbalanced diet high in carbohydrate and fat content Physical examination reveals the characteristic dermal and lingual lesions Atypical cases are many and can be recognized only by careful clinical study since there is no specific laboratory test for pellagra Were it not for the skin and oral changes characteristic of pellagra neither the typical nor the borderline cases could be distinguished from cases of chronic alcoholism beriberi pernicious anemia or sprue

Prognosis Pellagra is always a serious disease A favorable course depends on an early diagnosis followed immediately by intensive and persistent treatment If untreated or incompletely treated it usually becomes chronic and continues through remissions and recurrences until either the pellagra itself or a coexistent or resultant secondary disease produces incapacitation or death The disease tends to increase in severity with each attack but the author has observed recovery after thirteen distinct relapses Even in cases with rare recurrences the daily life of the patient must be properly regulated or he will fail to make satisfactory progress Without special treatment the death rate is more than 50 per cent in the severe cases Once the disease mild or severe has remitted the prognosis is good if no other predisposing condition or organic disease is present and provided the patient is cooperative and has perseverance to continue treatment

Pellagrins who seem to be making satisfactory progress often become suddenly worse and die No single manifestation can be used as the sole indicator of the prognosis In each case the immediate outlook is contingent upon the general condition of the pellagrin and upon the presence or absence of other diseases

The outlook is most grave when severe mental symptoms hallucinations violent motor excitement opisthotonos delirium rigidity tremors ankle clonus Babinski's sign or convulsions are present Extensive and severe gastrointestinal symptoms such as intractable diarrhea and vomiting severe glossitis stomatitis and cachexia may also have an unfavorable effect on the course of the disease Refusal of food long-continued abdominal distention and marked anemia should be regarded as ominous signs Pellagra is not usually accompanied by fever a temperature of 103 F makes for an unfavorable prognosis The danger is increased if chronic addiction to alcohol fatigue or surgical operations intervene The presence of infection darkens the outlook for just as infectious diseases predispose to pellagra so are pellagrins unusually susceptible to infections

Treatment Pellagra is a systemic disease and must be treated as such early promptly intensively and persistently The essence of successful treatment is improved nutrition adequate rest and good medical and nursing care The methods must be adapted to the special needs of each patient and can be carried out most effectively if the patient is hospitalized and placed under the direct supervision of a physician assisted by a nurse and a dietitian

Treatment of the Mild Case Every adult with mild pellagra must ingest and retain a well balanced high protein diet of at least 4000 calories per day the diet should include 1500 ml of sweet milk ½ pound of lean meat or liver and eight eggs Additional milk should be given instead of water except in very dehydrated cases Water tends to decrease the amount of food ingested the milk will not only supply fluid but will also be an additional source of nourishment Diets abnormally high in carbohydrate or fat content are contraindicated The diet should be supplemented especially at night by large amounts of a potent specific therapeutic agent prepared by a reputable concern When administered by mouth dry powdered brewers yeast (30 gm three times daily) wheat germ (60 gm three times daily) crude liver extract (30 gm three times daily) or niacin or niacinamide (10 doses 50 mg each daily) is effective The amide is preferable to niacin when one wishes to avoid vasodilating reactions

Treatment of the Severe Case The severe case that is one with central nervous system involvement intractable diarrhea persistent vomiting marked anemia a pulse rate exceeding 120 or a temperature of 103° F must have immediate supportive as well as antipellagric therapy As in the mild case success of treatment depends upon improved nutrition adequate rest and appropriate medical and nursing care The food intake must be increased to at least 4500 calories per day The specific therapeutic agent must be administered in amounts three times as large as those used for the mild case Absolute rest in bed is imperative Parenteral liver extract (probably the crude preparation is more efficacious that the refined) given intramuscularly in doses of 20 ml three to five times daily in addition to the wheat germ yeast or liver extract by mouth is often beneficial especially to patients with persistent vomiting or diarrhea Niacin orally (50 mg ten times daily) or niacinamide parenterally (50 mg in physiological solution of sodium chloride two or three times daily) is astoundingly effective Healing of the oral and dermal lesions even in the most severe cases usually begins within seventy two hours after treatment is begun and the relief of the psychoses of pellagra is spectacular

Special Treatment of Symptoms Symptomatic treatment often aids in remitting the disease Exacerbation of the stomatitis vomiting diarrhea and abdominal pain must not deter the physician from continuing the administration of proper diets specific therapeutic agents and indicated symptomatic therapy

ORAL LESIONS The use of a mouth wash is beneficial The teeth should be brushed gently to avoid severe hemorrhages

SKIN LESIONS Potassium permanganate solution (1 5000) used as soaks offers some relief and in the moist type of lesion diminishes the possibility of secondary infection

DIARRHEA Tincture of opium 2 ml can be given every four hours unless symptoms of overdosage appear This is sometimes beneficial and is particularly indicated whenever an analgesic is required The severe case should receive fluids by a parenteral route The administration of niacin is effective

VOMITING Absolute rest in bed and feed



Fig 61 Photograph showing symmetrical dry scaly pellagrous dermatitis on the feet of a Negro Note the sharply demarcated borders and the hyper pigmentation at the periphery of the lesions

ings of an iced fluid such as eggnog ginger ale or malted milk in small quantities (10 to 15 ml) at intervals of 10 to 15 minutes are necessary and should be continued until the patient has not vomited for 12 hours Yeast wheat germ or liver extract should be added to these feedings in amounts of 4 to 5 gm until the daily requirement has been given In the more severe case parenteral liver extract must be given immediately and continued until the patient is able to retain the required amount of the recommended diet together with any one of the potent specific therapeutic materials

MENTAL SYMPTOMS Large doses of niacin or niacinamide result in spectacular relief of the mental symptoms and their use is indicated instead of sedatives

PERIPHERAL NEURITIS Ice bags and local medications containing phenol (1 per cent) and menthol afford temporary relief Physical therapy and splints are often beneficial For use of vitamin B_1 see Beriberi

Prevention In order to eradicate pellagra persons with organic disease those who are poor chronic alcohol addicts food faddists and those with improper dietary habits must receive special attention

Organic Disease Organic disease often predisposes to pellagra by affecting the general nutrition and probably by increasing susceptibility Particular attention to the diet while the disease is being treated prevents the development of pellagra The incidence of pellagra is abnormally high among people having metabolic diseases chronic infections and diseases of the gastrointestinal tract

Poverty Although pellagra often develops as the result of financial inability to buy proper food lack of knowledge in regard to diet is an important contributing factor If sufficient amounts of a well balanced diet are eaten regularly pellagra will not develop Education of the poor in correct dietary habits is indicated so that those who can but do not may buy the inexpensive protective foods and those who cannot afford them may obtain protective substances such as yeast and wheat germ through relief agencies

Chronic Alcoholism Chronic alcohol addicts who do not eat adequate amounts of a well balanced diet acquire pellagra Alcohol alone does not cause the disease but it often decreases the patient s appetite and diminishes his food intake This is easily understood when we consider that often the heavy drinker receives from 3000 to 4000 calories per day from the alcohol alone When alcoholic pellagrins are induced to stop drinking their appetites return they eat more food and the disease is arrested and is not likely to recur Likewise alcoholic pellagrins who can be persuaded to eat large amounts of food do not have recurrences

Improper Dietary Habits It is a popular fallacy to believe that our customary diets are adequate Many people live on a diet of narrow range too high in fats and carbohydrates because of custom preconceived ideas as to what foods are good for one and dependence upon the appetite as the guide in the proper selection of foods Education of the masses in the essential dietary requirements is imperative

The pellagrin develops this disease because for one reason or another he does not get in his tissues sufficient niacin or materials which act similarly Large amounts of tryptophan can be converted into niacin Corn and corn products tend to be low in both salts of niacin and the amino acid tryptophan hence the association between the endemic pellagrin who eats a great deal of maize and maize products and his disease For over nine years the author has not seen a case of endemic pellagra in the southern part of the United States The disappearance of this disease which was so debilitating and rampant a few years ago has been due to the enrichment program to better dietary habits and to general interest on the part of the medical profession

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RIBOFLAVIN DEFICIENCY

The importance of riboflavin in human nutrition was observed *independently* by Sebrell and Butler and Vilter Vilter and Spies Riboflavin deficiency occurs in either sex at any age and is common in persons

who subsist over a considerable period of time on a grossly inadequate diet It tends to occur in the spring and to disappear during the summer months It is probably the most common clinically recognized deficiency disease in the United States

Diagnosis depends upon the recognition of characteristic angular stomatitis associated with transverse fissures in the corners of the mouth Another lesion occurring less frequently is the accumulation of greasy seborrheic material around the alae nasae and occasionally around the eyes and on the ears In the Nutrition Clinic of the Hillman Hospital Birmingham Alabama we have observed over 5000 persons with riboflavin deficiency The symptoms characteristic of riboflavin deficiency are angular stomatitis associated with transverse fissures in the corners of the mouth and lips and an abnormal shiny redness of the mucous membranes of the lips a shark skin appearance of the skin around the alae nasae and eyes and occasionally over the ears and malar prominences ocular symptoms characterized by bulbar conjunctivitis lacrimation burning of the eyes and failing vision and invasion of vessels of the cornea (Figs 55 56) An infrequent but spectacular lesion associated with deficiency of riboflavin in the tissues is termed the "magenta tongue It is characterized by flattening and mushrooming of the papillae giving the tongue a granular or pebbly appearance and a purplish red discoloration which has been attributed to dilatation and proliferation of the capillaries with slowing of the circulation These symptoms disappear within four to six days after the administration of adequate amounts of riboflavin

Treatment In the average case the administration of 5 mg of synthetic riboflavin three times a day was followed by the disappearance of the lesions within three to six days Two patients who were given 2 mg of synthetic phosphoric acid ester of riboflavin three times a day showed similar improvement within six to eight days In these cases Ashe and Spies found that the daily excretion of flavin (determined as riboflavin) was 18 per cent below normal Diminished output of flavin has been observed in other patients who have not had the typical lesions described After the administration of riboflavin the level in the urine rises These studies suggest that in persons subsisting on inadequate diets riboflavin deficiency is not uncommon Our figures indicate that the riboflavin requirement for an adult is approximately 3 5 mg daily

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ACRODYNIA

(Pink Disease)

Definition Acrodynia or pink disease is primarily a disease of infancy and early childhood characterized by painful red swollen hands and feet tachycardia hypertension hypomotility mental apathy anorexia and photophobia The onset is insidious and the disease may persist for months The outcome is favorable unless terminated by intercurrent infection

Etiology and Morbid Anatomy The disease is of unknown etiology It is impossible to trace familial incidence It usually occurs between the ages of four months and three years Transmission of the disease to other members of the family rarely occurs One theory is that it is the result of a dietary deficiency but it does not appear to be a deficiency of any of the known vitamins Another theory is that it is caused by a filterable virus but no virus has been isolated Histological studies show a degenerative process which affects both the central and peripheral nervous systems There is widespread peripheral nerve degeneration with demyelinization of the nerve sheaths The anterior horn cells and the cells of the posterior root ganglia often show chromatolysis It is possible that acrodynia includes a number of disease entities

Symptoms Because of the insidious onset the mother frequently cannot state (with any degree of accuracy) when the disease began In some instances the onset is associated with an upper respiratory infection or is manifested by cessation of growth and progressive loss of weight followed by fretfulness sleeplessness and refusal of food The child is excessively irritable and usually lies curled up in a knee elbow position with his face buried in

a pillow He constantly rubs together his reddened desquamating hands and when exposed to light he rubs his eyes He cries frequently especially when disturbed The cheeks are bluish red and in many cases the tip of the nose is red Areas of hyperemia alternating with ischemia appear on the skin of the hands and feet Papular rashes may appear over the whole body

Diagnosis The diagnosis is based on the presence of painful red hands and feet peeling of the skin prostration perspiration and photophobia accompanied by tachycardia and hypertension The most constant features of the disease are photophobia hypotonia and cutaneous rash The mild or borderline cases are not so clearly defined and in such instances diagnosis is more difficult The erythema in acrodynia however is readily distinguished from that of pellagra or the erythema caused by heat or cold

Prognosis Generally speaking the mortality rate is low When death occurs it is usually the result of an intercurrent infection

Treatment Ignorance of the true nature of the disease prohibits specific therapy In our Nutrition Clinic where several of these patients are treated each year we use two principles First we attempt the judicious use of barbiturates or other sedatives and we do everything possible to ensure the ingestion of a high vitamin high-caloric diet Secondly we give a mixed vitamin preparation containing 50 mg of niacinamide 5 mg of thiamine 5 mg of riboflavin and 50 mg of ascorbic acid in the babys milk three times a day At times we have given parenteral liver extract The mixed vitamin preparation and liver extract both *seem to give considerable symptomatic relief* It has recently been reported that *infusions of saline and the administration* of desoxycorticosterone acetate in debilitated infants with pink disease afford prompt improvement This is based on the presumed presence of adrenal insufficiency

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BURNING FEET SYNDROME

This disabling disease of nutritional origin was little known to American physicians prior to World War II It has been described under various names but has been noted in the Orient among underfed people for more than one hundred years Painful burning feet were so common among the prisoners of war in the Orient that sleep was practically impossible and walking difficult The patients improved slowly with general dietary improvement At best malnutrition and undernutrition are associated with this syndrome because it appears only among groups on very restricted diets The incidence of endemic nutritive failure among the population of the southeastern United States where the author has worked so long has decreased greatly in the past twenty years When the incidence was high burning feet was a common presenting symptom of the patients Many but not all of them could be relieved by the administration of thiamine In recent years the general nutrition of the population has improved and the physician rarely sees persons who complain of burning feet arising from general dietary failure A number of observers have been able to relieve the so called "burning feet syndrome" by the administration of pantothenic acid

PANTOTHENIC ACID DEFICIENCY

Pantothenic acid is an integral part of coenzyme A and therefore is essential for cellular metabolism Uncomplicated pantothenic acid deficiency has not been observed in man as this vitamin is present in all food and may be synthesized by intestinal bacteria Bean and co workers attempted to induce a pantothenic acid deficiency by the administration of omega methyl pantothenic acid to human volunteers and by deleting the vitamin from a highly purified diet The subject given the pantothenic acid antagonist developed easy fatigability somnolence paresthesias of the hands and feet abnormalities of gait dizziness postural hypotension tachycardia epigastric distress increased incidence of respiratory infections and changes suggestive of adrenal cortical insufficiency The symptoms were not relieved completely by the administration of pantothenic acid and could not be reproduced when the diet was low in this vitamin

Frequently the "burning feet syndrome is associated with pantothenic acid deficiency

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PYRIDOXINE (VITAMIN B_6) DEFICIENCY

Between 1951 and 1953 many physicians throughout the United States observed that artificially fed young infants taking a pyridoxine (vitamin B_6) deficient formula developed hyperirritability and convulsive seizures These clinical observations provided much important information It was soon recognized that in each case there was a uniform pattern of symptoms varying in degree of severity The convulsions were unassociated with any other signs of illness and there were no physical findings or laboratory abnormalities indicative of any etiological factor The infants had normal birth histories and had grown and developed normally until they were at least eighteen weeks of age The onset of the convulsions was sudden All the physicians reporting their occurrence found that the infants invariably had been fed on a commercial liquid formula which consisted of defatted cows milk vegetable and animal fats vitamins and iron No cases were encountered in which the infants received the powdered formula which contained pyridoxine When the infants were fed the powdered formula or when they were given supplementary foods such as cereals meats fruits and vegetables or when they were given pyridoxine either orally or by injection the convulsions disappeared and did not recur if a supplement of pyridoxine was continued

Pyridoxine deficiency in adults has been induced experimentally by Mueller and Vilter through the administration of desoxypyridoxine a metabolic antagonist of pyridoxine The clinical manifestations included the development of a seborrheic like dermatitis about the eyes nose and mouth a cheilosis which resembled that of riboflavin deficiency and a glossitis which was morphologically similar to that of niacin deficiency The skin mucous membrane and lingual lesions remained unchanged when thiamine riboflavin and nicotinamide were given but disappeared promptly following the administration of pyridoxine

Although far too little is known regarding the function of pyridoxine in human beings its essential function had been demonstrated previously Many years ago an etiological relationship was established between pyridoxine deficiency and convulsive seizures in rats chicks and pigs Synthetic pyridoxine was first administered to human beings in 1939 by Spies Bean and Ashe who stressed that after the deficiencies of niacin riboflavin and thiamine were corrected and if the patients remained on their deficient diets pyridoxine would produce an additional improvement Snyderman and associates and Stokes and associates (quoted by Coursin) have made interesting observations on single patients suggesting a relationship between pyridoxine deficiency and convulsive seizures

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VITAMINS (FOLIC ACID AND VITAMIN B_{12}) AND BLOOD REGENERATION

Folic acid pteroylglutamic acid appears to be biologically active in the form of 5 6 7 8 tetrahydrofolic acid In this reduced form it serves as a carrier of a one-carbon unit (C_1) on the oxidation levels of formaldehyde and formate The combination of tetrahydrofolic acid and C_1 is in the form of the N^{10} formyltetrahydrofolic acid or of the bridged N N^{10} methenyl or methylene derivatives these biologically active forms probably give rise nonenzymatically to N formyltetrahydrofolic acid a stable compound known as folinic acid or citrovorum factor The transfer of a C_1 unit is involved in the following metabolic functions of folic acid (1) the incorporation of C_1 into the 2 and 8 positions of purines (2) the formation of the methyl groups of methionine choline and thymine (3) the synthesis and catabolism of serine and histidine and the catabolism of tryptophane Although these activities are probably not the sole functions of folic acid it is clear that a deficiency of folic acid will have widespread and diverse metabolic effects

Vitamin B_{12} cyanocobalamin was first isolated from liver by Rickes Folkers and their associates in the United States and independently by E Lester Smith in Great Britain It consists of (1) a planar porphyrin like moiety with a cobalt atom in its center (2) cyanide bound to the cobalt (3) 5 6 dimethyl benzimidazole ribotide and (4) 1 amino 2 propanol The metabolic functions of vitamin B_{12} are not clearly delineated Claims have been made for its role in the reduction of disulfide linkages to

sulfhydryl groups in thymidine and deoxyriboside synthesis in methyl group formation and in protein synthesis A conclusive definition of its metabolic functions however remains to be accomplished

Folic acid was the first of many synthetic chemical substances shown to produce blood regeneration in persons with pernicious anemia nutritional macrocytic anemia macrocytic anemia of pregnancy macrocytic anemia of sprue and megaloblastic anemia of infancy Soon it was demonstrated that folic acid failed to protect against or to prevent the symptoms arising from acute degeneration of the spinal cord so frequently associated with pernicious anemia and it became clear that folic acid was not a complete therapeutic agent for the treatment of pernicious anemia but that it is an essential therapeutic agent for the treatment of the average case of macrocytic anemia of pregnancy and megaloblastic anemia of infancy It is a useful therapeutic agent in the treatment of sprue and nutritional macrocytic anemia

Folic acid is an important member of the vitamin B complex The administration of folic acid or foods which contain it to expectant mothers whose diets are low in folic acid is mandatory In this way the macrocytic anemia of pregnancy infancy and early childhood can be prevented It is recommended that at least 2 mg per day be administered in the last third of pregnancy if the diet is deficient in folic acid It is interesting to note that the mother can concentrate folic acid and transmit it through her milk to the infant so as to produce a therapeutic response in the infant with megaloblastic arrest

During the past eight years by administering folic acid as a supplement to the diet we have enabled numerous patients to continue working These patients had tropical sprue or nutritional macrocytic anemia were totally incapacitated and probably would have died if specific therapy had not been administered either orally or parenterally The precise dose of folic acid varies from patient to patient but in the average case 5 to 10 mg per day and usually much less produces a prompt hemopoietic response which is paralleled by a striking clinical response The glossitis heals the patient s appetite increases and his strength rapidly increases

The bone marrow biopsy and peripheral blood findings in pernicious anemia are indistinguishable from those found in nutritional macrocytic anemia tropical sprue and nontropical sprue in relapse and the administration of vitamin B_{12} is effective in each of these conditions A number of types of steatorrhea which sometimes are associated and confused with endemic sprue as a rule are not relieved by this material It should be emphasized that the average patient who receives vitamin B_1 should receive it parenterally or orally in association with an active intrinsic factor Parenteral therapy is effective in a higher percentage of cases When given in small doses by mouth vitamin B_1 does not usually benefit persons with pernicious anemia in relapse unless an intrinsic factor is added

Pain tingling numbness and stiffness of the extremities develop when there is a deficiency of vitamin B_1 and this condition may advance to complete or partial paralysis The symptoms can be ameliorated when treated promptly by injections of vitamin B_1 The chronic phase of the disease does not respond well to treatment

TOM D SPIES

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Vitamin C Deficiency

(Scurvy)

Scurvy is a nutritional disorder caused by prolonged inadequacy of the supply of *ascorbic acid* Mild symptoms include apathy anorexia fatigability and loss of strength in more severe cases there is tenderness of the extremities and gums together with a hemorrhagic tendency The manifestations of the disease depend on the age of the patient Infantile scurvy

differs from adult scurvy principally in the extent to which the growing bones are involved

History The name scurvy" appeared first in the Middle Ages as a folk word having various forms phonetically allied in several European tongues The Latinized scorbutus is an artificial implant

Possibly the earliest clear-cut description of the disease was made by de Joinville among Crusaders of the thirteenth century To Joseph Lind an officer of the British navy belongs the credit of amassing convincing evidence first that scurvy is a disorder of nutrition and not a contagion or strictly an occupational disease and second that it results not from excessive consumption of certain articles of diet but from insufficient intake of others His Treatise on the Scurvy published in 1753 was ultimately responsible for the introduction of lemon juice into the seaman s ration Even well into the twentieth century scurvy continued to threaten the success of voyages of discovery and to stalk the victims of blockade siege and shipwreck

Scurvy was produced in laboratory animals by Holst and Frolich whose studies were published in 1907

In 1928 Szent Gyorgyi isolated from the suprarenal glands of oxen and from various plant sources a crystalline compound of formula $C_6H_8O_6$ which he named hexuronic acid The wide distribution of this compound in animal tissues and in growing plants was soon appreciated as were also its strong reducing properties but it was not until 1932 that Szent Gyorgyi determined by appropriate feeding experiments that he had been dealing with the specific antiscorbutic factor vitamin C Simultaneously and independently King and Waugh isolated a highly active antiscorbutic compound from lemon juice and showed that it was identical with hexuronic acid By common agreement the latter term *was abandoned in favor of ascorbic acid*

Etiology Ascorbic acid is essential for the proper formation of collagen by fibroblasts and there is evidence that it participates in the production of intercellular material in other tissues such as the cement substance of vascular endothelium and the attachment of striated muscle cells to tendon Together with its oxidation product dehydroascorbic acid it constitutes within the body an important oxidation reduction system Through its function as a hydrogen donor ascorbic acid serves in converting folic acid to the physiologically active folinic acid In the absence of ascorbic acid the metabolism of aromatic amino acids especially of tyrosine and phenylalanine is disturbed Several additional roles in intermediary metabolism have been suggested but less reliably documented

Fresh fruits vegetables and raw meats contain ascorbic acid in sufficient quantity to prevent the appearance of scurvy if the diet is composed largely of uncooked or freshly cooked natural products The juice of ripe oranges has a fairly constant content of ascorbic acid at about 0 5 mg per ml Other citrus fruits though showing greater variation under market conditions contain similar quantities In general the ascorbic acid content of plant tissues parallels their store of carotenoids or chlorophyl green leaves and shoots of all kinds as well as tubers whether edible or those generally regarded as inedible are sources of vitamin C

In animal tissues the concentration of ascorbic acid is highest in adrenal hypophysis corpus luteum lens and aqueous humor and somewhat less in brain pancreas liver spleen and kidney it is considerably lower in muscle tissue distinctly low (about 0 5 to 1 5 mg per 100 ml) in blood plasma and virtually absent from fat Cow s milk as processed for urban consumption does not provide a reliable dietary quota of vitamin C Chemical synthesis of ascorbic acid from sorbitol is now more economical than is its extraction from natural sources

The human organism lacks the enzyme system required for the conversion of L gulonolactone to ascorbic acid an essential step in the biosynthesis of vitamin C and consequently depends on extraneous sources for its essential requirements If the supply is cut off for a sufficiently long time a matter of months clinical scurvy supervenes In times of peace and normal economic life the disease is seen as a rule only in recluses and faddists who from ignorance boredom or fear of infection confine their diet essentially to heated oxidized and therefore ascorbic acid free foods

The minimal daily requirement of ascorbic acid has not been accurately determined A group of British volunteers remained in good health when on a daily intake of as little as 10 mg for nine months and as a result British nutritionists commonly cite 30 mg as the minimal daily intake needed American authorities on the other hand usually quote a higher figure of the order of 1 mg per kg or for an average adult 75 mg per day Even on a daily intake of this size there is no assurance that the body s capacity to utilize ascorbic acid has been exceeded for with additional dietary load retention continues for a time until loss through urinary excretion takes place above a threshold level of approximately 1 5 mg per 100 ml of plasma On an average diet the normal adult excretes from 5 to 50 mg of ascorbic acid in the urine in twenty four hours An increase in the intake augments this output though

not immediately and not quantitatively If to an average diet one adds a daily supplement of 500 mg of ascorbic acid urinary excretion of the vitamin will rise significantly within the first or second 24 hour period and will level off at about 80 per cent of the intake After this equilibrium has been established withdrawal of the supplement results in a similarly steep falling off of excretion so that within three or four days the output has returned to the starting level It would seem in other words that the organism has a limited capacity for storing vitamin C that on an average diet the stores are not filled to the saturation point and that after saturation the major portion of the intake is excreted by the kidneys

Infections and other forms of "stress" rheumatic activity and hyperthyroidism accelerate vitamin C depletion Withdrawal of ascorbic acid from the diet of a normal subject for a period of one or two weeks causes a clearly detectable change in the economy of the vitamin when a supplement is subsequently added the daily administration of a liberal quantity of ascorbic acid after such a vitamin free period may fail to produce an increased output in the urine for four days or even longer

In scurvy the body stores of ascorbic acid are significantly depleted the plasma concentration is zero or nearly so and the small quantities reported present in urine may well reflect merely the error of analysis In the depletion process the white blood cells and platelets which normally contain ascorbic acid at a concentration some thirty times as great as that of cell free plasma retain their stores with relative avidity yet they likewise lose their ascorbic acid by the time symptoms appear On administration of the vitamin relief of symptoms and signs of scurvy precedes the restoration of a normal urinary output of ascorbic acid or the establishment of a stable plasma concentration at a normal level

The time required to bring out symptoms of scurvy on a deficient diet varies greatly in ordinary clinical circumstances since complete deprivation is seldom encountered except under experimental conditions and since the intake of even a small quantity of the vitamin tends to delay the onset of symptoms In a notable human experiment carried out by Crandon under controlled conditions of strict dietary deficiency the subject s plasma level of ascorbic acid fell to zero by the forty first day the white blood cells and platelets became depleted after four months yet objective signs of scurvy in the form of cutaneous hemorrhages were not evident until the 161st day of the experimental diet These intervals presumably represent approximately minimal values Subjective symptoms of a less specific nature—languor fatigability and anorexia—preceded the appearance of objective signs

Most cases of scurvy seen in infancy develop six months or so after the institution of artificial feeding A few examples have been reported in infants considerably younger but in these instances the mother could invariably be shown to have subsisted on an inadequate diet during pregnancy and since the concentration of ascorbic acid in fetal tissues is directly influenced by the mother s diet the period of vitamin deprivation as it affected such a mother s infant obviously commenced before birth The concentration of ascorbic acid in human milk while invariably higher than that in maternal plasma closely reflects the adequacy of the mother s intake

Pathology The gross morbid anatomy of scurvy is largely that of the associated hemorrhages In the skin these may be ecchymotic or petechial Minute extravasations often dot the hair follicles of exposed or dependent parts while larger ecchymoses are found in regions subjected to trauma Subcutaneous fascial or intramuscular hemorrhages may occupy sites of particular mechanical stress

Subperiosteal hemorrhages are relatively uncommon in adult scurvy but invariably accompany severe cases of infantile scurvy owing to loosening of the periosteal attachment which is a primary feature of the functional pathology of the disease capillary bleeding may dissect the periosteum free over a large area Most commonly these subperiosteal hemorrhages are found at the lower end of the femur the upper end of the humerus both ends of the tibia and at the costochondral junction of the middle ribs

In growing bones the histopathology of scurvy is distinctive revealing a suppression of the orderly growth process and of the normal conversion of cartilage matrix into bone In addition hemorrhages may be found in the interior of the bone at the cartilage shaft junction together with fractures of the minute columns of cartilage matrix and at times dislocation separation or impaction of the epiphysis

The lesions of the gums will be described

among the clinical signs Scurvy causes striking changes in the teeth separation of the odontoblast layer from the dentin and development of hemorrhages within the pulp cavity Although the teeth are capable of functional recovery the healing process is never anatomically complete so that histological identification of an antecedent attack is possible throughout life

The effects of suppression of collagen formation become evident in experimental studies of wound healing such as those which Crandon added to his self imposed nutritional privations By the time hemorrhagic manifestations of scurvy had appeared a little more than five months after initiation of the C free diet a freshly inflicted surgical incision showed no evidence of organization for some days until the administration of ascorbic acid started the healing process on its normal course

Symptoms The symptoms of the disease begin as a rule insidiously with a feeling of general weakness and inadequacy negativism depression or even melancholia The normal degree of alertness is replaced by a disposition to inactivity Appetite fails and the taking of food is additionally hampered by painful gums which are disposed to bleed easily The skin is dry and rough with prominent gritty follicles In areas in which capillary pressure is high as in the lower extremities or in regions distal to constricting bands of clothing minute hemorrhages are to be seen in the hair follicles

Increasing mental depression accompanies progressive loss of muscle power The lips become cyanotic and the gums begin to show erosion of the mucous membrane at their margins with formation of friable clots adherent to the teeth almost invariably these are accompanied by fetid breath The lower extremities develop swellings in the muscle masses particularly in the extensors and adductors of the thighs and in the calves and the knees are held in partial flexion efforts toward full extension are accompanied by pain There is increased swelling of the subcutaneous tissue of the feet particularly between the Achilles tendon and the tibia Tenderness on deep pressure may be elicited in any part of the limb Finally ecchymoses appear especially over the lower third of the thigh above the malleoli or on the dorsa of the feet Hemorrhage into the muscle masses or beneath the periosteum is generally accompanied by induration There may be either microscopic or gross hematuria Not all the symptoms mentioned are necessarily of simultaneous occurrence Mental depression is rarely absent but ecchymoses may occur in the absence of stomatitis and the disease may be clinically recognizable before extensive intramuscular or subperiosteal hemorrhages have taken place

With healing recovery occurs in more or less the following order stomatitis mental depression induration cutaneous hemorrhages and last follicular keratosis

In particularly severe cases the course is progressively downhill The teeth loosen and fall out often with uncontrollable hemorrhage There may be hemorrhage from the nose stomach or intestines or an extravasation of blood may suddenly appear without provocation at some bizarre site as in the orbit causing proptosis and ecchymosis of the eyelids The pulse becomes rapid and weak and the patient may suddenly die from relatively mild physical exertion or may expire from progressive prostration or intercurrent infection

In infants apathy and irritability alternate but anorexia is the rule In contrast to the afebrile state of older patients elevation of temperature is almost always present Petechial hemorrhages are generally less conspicuous than in the adult The tenderness of the involved extremities and the changes in contour brought about by subperiosteal hemorrhages and epiphyseal infraction are often extreme On the other hand the oral signs are usually limited to swelling and purple discoloration of the gums around deciduous teeth which have already erupted or are about to erupt while the formation of large vegetations is rare and fetor exceptional Anemia of some degree is almost always found The leukocyte pattern is not affected in uncomplicated cases

Scurvy often goes hand in hand with other deficiency diseases

Diagnosis The diagnosis of scurvy is generally made on the history of an inadequate diet combined with the detection of some of the more obvious physical manifestations of the disease Bleeding which does not depend on some demonstrable cause must arouse suspicion Tenderness may be confined to the region of the long bones of the lower extremities or may at times be so capricious in its orientation as to bring the patient under suspicion of neurosis or even malingering The changes in the gums produced by scurvy may be simulated in thrombocytopenic purpura leukemia or

mercurial poisoning In infants the roentgen picture in the long bones is pathognomonic but in children and especially in young adults this diagnostic aid is less helpful Subperiosteal hemorrhage is not ordinarily recognizable in roentgenograms until some days after the institution of effective therapy and until the formation of new bone has been resumed in the elevated periosteum Demonstration of capillary fragility is suggestive but must be supported by more specific evidence

Biochemical assay of the ascorbic acid stores plays a salient part in diagnosis A plasma level close to zero accompanies all cases of untreated scurvy but identical values may be found in many subjects who are symptom free and who in consequence cannot be described as scorbutic The same may be said of low urinary concentrations Accurate evaluation of the degree of depletion may be achieved in any of three ways (1) simultaneous determination of the concentration of ascorbic acid in the patient s plasma and in the white cell and platelet layer of centrifuged blood (2) measurement of the plasma level in the fasting state and after intravenous or intramuscular administration of a test load of ascorbic acid (3) daily estimation of the total urinary excretion of ascorbic acid for several days after liberal dosage of the vitamin (of the order of 500 mg daily) Depleted stores are indicated in (1) by low values in both determinations in (2) by a low flat 4 hour curve in (3) by a delay of two days or more in the rise of urinary excretion

Since the response of a scorbutic patient to specific antiscorbutic therapy is usually prompt and dramatic a simple therapeutic diagnostic test is rational and often decisive

Prognosis Scurvy is readily amenable to treatment provided it is recognized in time Convalescence prolonged more than a month after the institution of adequate antiscorbutic therapy usually reflects the presence of some additional dietary deficiency e g protein thiamine riboflavin or niacin Conspicuous as is the tendency to hemorrhage in the symptomatology of the disease fatal bleeding is rare

Treatment In a therapeutic test for diagnostic purposes the daily administration of 250 mg of ascorbic acid may be expected to dispel anorexia relieve mental depression to a considerable degree eliminate tenderness of the extremities and obviate the appearance of fresh capillary hemorrhages within two days to a week provided these symptoms have their origin in a deficiency of vitamin C The total quantity of ascorbic acid required to resaturate a scorbutic patient varies from about 2 gm up to ten times that amount Absorption of orally administered ascorbic acid is usually complete or nearly so appreciable reduction in absorption occurring only in the presence of diarrhea or chronic disease of the intestinal tract Solutions of ascorbic acid are well tolerated in the blood stream as much as 6 gm having been given in a single dose without adverse effect In spite of its acidity a 1 or 2 per cent solution of ascorbic acid in normal saline need not be buffered or neutralized for intravenous injection

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Vitamin D Deficiency

(Privational Rickets)

Definition Privational rickets is a disease characterized chiefly by clinical and roentgenologic abnormalities of the skeleton which result from deficient deposition of lime salts in growing cartilage and in newly formed bone It is a deficiency disease caused by insufficient vitamin D during the age when growth is rapid Since the human organism is able to supply its need for the vitamin either by ingestion or by autosynthesis in the presence of sunlight rickets is an expression of the combined absence of two factors one dietetic and the other environmental

Incidence The disease primarily affects infants at the age when rapid growth is taking place Several months must usually elapse before the manifestations are per

ceptible clinically the disease is therefore extremely rare in the early weeks of life and the majority of cases are diagnosed between the ages of four months and two years Formerly the incidence was exceedingly high Observations in different places indicate that from 50 to 98 per cent of the infant population was affected Today in the United States the widespread use in infant feeding of milks fortified with vitamin D has had an amazing effect in lowering the incidence In most areas severe rickets is a rare disease It is observed more commonly in breast fed than in artificially fed infants

The premature infant is particularly susceptible to rickets The susceptibility is so extreme that one is almost justified in saying that moderate or severe rickets will develop in all premature infants unless preventive measures are instituted Twins belong in the same category

Rickets is predominantly a disorder of the temperate zone It is rare in the far North where fish constitute the chief source of food the influence of sunlight prevents its occurrence in the tropics There is a seasonal incidence in the Northern Hemisphere the peak occurs during the winter and spring months when the rays of sun from the south are slanting Environmental variations in the amount of exposure to the sun also account for a greater prevalence in urban than in rural communities The Negroes and Italians who dwell in the cities of the United States are unusually susceptible to rickets the susceptibility is accounted for at least in part by the dark pigmentation of the skin which offers a barrier to the penetration of radiant energy

Pathology Distinctive findings are limited to the skeleton and result chiefly from the failure of deposition of lime salts in growing cartilage and in newly formed bone The uncalcified bone or osteoid tissue is morphologically similar to normal bone but because it lacks the elements essential for rigidity it is soft and easily distorted In health the formation of new bone is greatest at the ends of the long bones and at the costochondral junctions in these places rickets produces the greatest change Calcification fails in the zone of proliferating cartilage cells which then persist in scattered tonguelike aggregations Capillaries from the shaft invade the region between cartilage cells and carry with them an envelope of connective tissue Thus the regular epiphyseal line" of health disappears and in its place there develops a zone composed of osteoid and connective tissues blood vessels and cartilage cells This is the rachitic metaphysics It is soft and in response to external stress the bone will bend in this region The constant pull of muscles and tendons tends to mushroom the firm epiphyseal cartilage into the metaphysis The resulting increase in circumference is the epiphyseal enlargement of rickets

Evidence of the disorder is also found in the shafts In healthy bone the process of destruction by osteoclasts and replacement by osteoblasts is continuous in rickets the process is similar except that replacement is by osteoid rather than by osseous tissue Trabeculae of bone come to be enveloped by a mantle of osteoid tissue Fractures are frequently found In health the production of cortical bone is a function of the periosteum In rickets the periosteum is sometimes excessively active in laying down concentric layers of lime deficient bone so that the shaft becomes considerably increased in thickness

When rickets begins to heal the first change results from calcification of the matrix about the more recently differentiated cartilage cells The new epiphyseal line which is formed is demonstrable by roentgenogram and demarcates the distal end of the rachitic metaphysis The hiatus *which remains between the new line and* the shaft is obliterated more slowly

Etiology *Metabolic and Chemical Aspects* Vitamin D has a profound effect both on the absorption of calcium and phosphorus from the intestine and on the reabsorption of phosphorus by the renal tubules During rickets large amounts of ingested calcium and phosphorus are excreted in the stools With healing a strongly positive balance is established until the skeleton has been replenished Thereafter the larger part of the excess phosphorus over that required for growth is excreted in the urine while the bowel continues to be the principal route for eliminating calcium

The serum of healthy infants normally contains per 100 ml 10 to 11 mg of calcium and 4 5 to 5 5 mg of inorganic phosphorus According to Howland and Kramer the product of the calcium and phosphorus when both are expressed in milligrams per 100 ml furnishes an index of the presence or absence of rickets A product less than 30 indicates the presence of rickets a product between 30 and 40

may or may not be associated with rickets a product greater than 40 indicates either that rickets is absent or that the disease is undergoing healing In most cases of rickets the low product results from a deficit in inorganic phosphorus When tetany complicates rickets the calcium level is affected chiefly *

Symptoms and Physical Signs The accuracy which the roentgenogram has contributed to the diagnosis of rickets has made it clear that the only characteristic signs are those which pertain to the skeleton Other manifestations such as irritability excessive sweating or muscular hypotonia are either difficult to evaluate or common to so many disorders as to be of no aid in recognizing the disease As a single exception the manifestations of tetany during infancy strongly suggest the presence of rickets Tetany however is a complex of symptoms which accompanies only a small fraction of all cases of rickets and which may occur from causes other than those responsible for rickets The skeletal signs of rickets are the combined result of the softened state of bone in the regions where growth is occurring and of the external stresses to which these regions are exposed Since age is a factor in determining the sites of rapid growth and since new stresses come into play when the child learns to sit and to stand it is apparent that the manifestations of rickets must vary in relation to the age at which they develop Long after the disease has ceased to be active the residual deformities are evidence of the age at which the process was most intense

Craniotabes may be the earliest demonstrable sign of rickets it is rare after the eighth or ninth month of life It develops in the occipital or parietal bones in one or more areas removed from the lambdoidal suture and invariably on that side of the head upon which the infant has habitually lain It is usually associated with softening along the suture line Craniotabes is often overlooked on routine physical examination its presence is detected by pressure with the finger over the probable sites of involvement and the finding of relatively soft areas where the skull buckles and snaps back when the pressure is released The sensation is much the same as one experiences when pressing on a celluloid ping pong ball As the infant approaches the end of the first year of life craniotabes generally disappears even though the rickets continues to be active By this time however the skull may present other evidence of the disease The eminences of the frontal and parietal bones become unusually prominent and later are thickened into actual bosses which produce a square head (*caput quadratum*) Sometimes the eminences stand out as four rounded elevations separated by depressions which mark the lines of sutures (*hot cross bun* head *caput natiforme*) Rickets also results in delayed closure of the fontanels In severe cases the anterior fontanel may still be membranous at the age of three or four years

Thoracic deformities belong among the early signs of rickets Rapid growth of the ribs during infancy renders the costochondral junctions particularly the sixth and seventh unusually susceptible Here rounded enlargements make their appearance and can be palpated along a line which extends downward and laterally on either side of the chest This is the *rachitic rosary* As the disease progresses the weakened metaphyses of the ribs yield to the force of negative pressure in the thorax and bend inward When the enlargements at the rib-cartilage junctions are palpable externally they are even more prominent on the inner wall of the thorax Finally an external groove or depression develops along the line of the rosary At its lower end the groove merges with a girdle like depression (*Harrison s groove*) which appears when the ribs have bent inward along the attachments of the diaphragm Harrison s groove is generally accentuated by flaring of the lower ribs and distention of the abdomen Park and Howland have pointed out that the functional embarrassment which attends severe rickets of the thorax may actually endanger life The thoracic cage instead of expanding with each downward excursion of the diaphragm may even become more constricted pulmonary ventilation is further reduced by wide areas of atelectasis respiration is rapid and difficult and a relatively mild infection may have a fatal termination

Enlargements at other epiphyses develop more slowly than at the costochondral junctions but are often well developed before the end of the first year of life They are recognized most easily at the

Rickets of etiology other than vitamin D deficiency is discussed elsewhere in the text under the headings of Fanconi Syndrome Phosphorus Diabetes Vitamin D Resistant Rickets Hypophosphatasia Tubular Acidosis Cystic Fibrosis Cystinosis and Renal Rickets"

wrists and ankles where the subcutaneous tissue is relatively thin When the swelling is slight it is difficult to be sure that one is not dealing with the normal protuberances of the malleoli or styloid processes In examining the wrist the writer has made it a practice to palpate the dorsal as well as the lateral aspects since an abnormal swelling at the former surface is less liable to be confused with normal styloid processes Another type of bony enlargement may result from excessive production of subperiosteal bone In the hands it leads to fusiform enlargement of the proximal and middle phalanges (*string of pearls* deformity)

Most conspicuous among the permanent malformations caused by rickets are the *bending* deformities To a large extent they originate when the disease continues to be active after the child has learned to sit The rachitic child shows little inclination to engage in the incessant activity which characterizes his healthy peers a posture once chosen becomes habitual and he sits for hours in essentially the same position The resulting stress on the skeleton leads to deformity not only because the bones are unusually yielding but also because the direction of application is unusually constant Commonly the child sits with thighs slightly spread apart and with one lower leg crossed over the other the hands are placed on the floor or on the thighs to assist the spine in holding the trunk erect The pull of gravity on the foot is augmented by that of the Achilles tendon so that the lower epiphyses of the tibia and fibula are displaced backward producing an angular deformity (*saber shin*) At the time of its origin the maximal convexity is just above the ankle With increasing age the bones grow in length beyond this site and ultimately the greatest bend is about one third the way up the shaft of the tibia Stress on the femur from the same posture leads to lateral and forward bowing and the femoral head is bent forward toward the shaft (*coxa vara*) That portion of the spine which is unsupported by the thorax is unusually vulnerable and marked lumbar kyphosis is not uncommon The combined deformities of lumbar kyphosis pot belly and flattened thorax produce a striking picture when the child is viewed in profile the outline is that of an erect truncated cone with the base at the level of the navel Less conspicuous bending deformities may develop in the upper extremities The humerus bows outward and the lower epiphyses of the radius and ulna may be bent to one side or the other depending upon the direction in which the hands are habitually turned When the child with rickets has learned to stand the stresses are altered Kyphosis is replaced by lumbar lordosis coxa vara is increased and bow legs or knock knees make their appearance The significant rachitic flattening of the pelvis probably begins during infancy from the force of gravity and is increased by the stresses applied during sitting and standing

Diagnosis by Roentgenogram The roentgenographic changes characteristic of rickets are most easily recognized in pictures of the lower ends of the radius and ulna The earliest changes are seen almost exclusively at the *cartilage shaft junction* The normally sharp termination of the shaft becomes blurred and finely irregular (*fraying*) the line of termination tends to become concave (*cupping*) the end of the bone is widened (*spreading*) and in some instances *cortical spurs* may be present at the lateral margins where lime salts have been deposited in the perichondrium which is adjacent to the periosteum As the disease progresses to the moderate and more severe stages the alterations become unmistakable The spreading increases the end of the shaft is hollowed out into a crater and the fraying widens into a fringe which may be 1 cm or more in width Severe rickets is also attended by distinctive roentgenographic findings in the shaft These include marked osteoporosis either thinning or sometimes a lamellated type of thickening of the cortex and cloaking of the shaft with rarefied subperiosteal bone Change in the shaft however is rarely useful in establishing an early diagnosis and is a less sensitive index of the progress of successful therapy than is the cartilage shaft junction

The beginning of healing is heralded in roentgenograms by the appearance of new deposits of lime salts in the zone between bone and cartilage Particularly prominent is the reappearance of an *epiphyseal line* at the proximal boundary of the cartilage At this stage the end of the bone is marked by two horizontal lines between which the area of greatest disorder is isolated The *final obliteration of signs* of the disease in roentgenograms may require many months

Prophylaxis and Treatment The Food and Nutrition Board of the National Research Council has recommended that normal infants receive a daily dosage of 400

to 800 international units of vitamin D Vitamin D milks either fresh or recon stituted from the evaporated state furnish about 400 units per quart Full term infants reared from birth on formulas made from vitamin D milk do not acquire clinically detectable rickets mild roentgenologic rick ets if it develops disappears as growth continues Since young infants ingest less than a quart of milk a day and because the deleterious effect of slight vitamin over dosage is unimportant most physicians prescribe a small supplement

Cod liver oil to be acceptable by the U S P must contain 85 units of vitamin D per gram (400 units per teaspoon) the products of the better pharmaceutical houses are generally more potent Concen trates contain from 50 to 300 units per drop The physician should be aware of these variations in prescribing dosage In fants on formulas made from vitamin D milk do not derive benefit from a supple ment of more than one teaspoon per day of cod liver oil of minimum U S P strength for infants on nonenriched formulas two teaspoons are ample When concentrates are used the dose must be measured in drops

When active rickets must be treated or when the disease is to be prevented in pre mature infants one of the many available concentrates should be prescribed Dosage in the neighborhood of 5000 units daily is satisfactory

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Vitamin E Deficiency

In 1922 Evans and Bishop first demon strated the existence of this vitamin Five years later Evans and Burr wrote a mono graph on the subject which is the founda tion of our knowledge today

The term "vitamin E" has been applied to alpha tocopherol and to a lesser extent to the other tocopherols and certain syn thetic substances which restore fertility to the vitamin E depleted rat Vitamin E is synthesized in plants The vegetable seed oils such as wheat germ oil and cotton seed oil contain tocopherols In 1936 Evans Emerson and Emerson isolated three to copherols alpha beta and gamma

Experimental studies on animals carried out under standardized conditions have produced distinct results Symptoms of vita min E deficiency appear earlier in the male than in the female rat The weight of the testes decreases and spermatozoa become nonmotile In the female the fetuses die young if the deficiency is mild if it is greatly advanced absolute sterility occurs In rats and rabbits on a vitamin E deficient diet one of the earlier signs is a dystrophy of the striated muscles and greatly in creased urinary creatine After the admin istration of vitamin E the creatine content of the urine decreases promptly No such definite changes have been found in the urine of man with any neuromuscular dis turbance Vitamin E has a remarkable in fluence on the storage of vitamin A in experimental animals It is widely employed as an antioxidant

Experimental studies on human beings have not yet demonstrated sufficient useful ness of vitamin E to warrant making defi nite claims as to its role in human nutri tion It is claimed that it has a beneficial effect in habitual abortion and it has been reported to be beneficial in primary fibro sitis These claims have not been substanti ated however Harris Hickman Jensen and Spies have shown that the plasma level of tocopherols is lower in persons with nu tritional deficiency diseases than in well nourished persons That the administra tion of vitamin E produces no harmful effects has been observed by the writer who administered 100 mg daily to patients for three months without untoward symptoms

Much work on the action of vitamin E has been carried out but its fundamental action in the human body remains obscure We know practically nothing of either man s requirement for it or its biological action in human beings Many of the studies re ported have been poorly controlled and their evaluation has been uncritical

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Vitamin K Deficiency

Definition Deficiency of vitamin K is characterized by a hemorrhagic diathesis caused by a lowered blood prothrombin level which is detectable as an increase in the prothrombin clotting time The disease occurs primarily in patients with jaundice or certain intestinal disorders and in the newborn infant It is not a true primary dietary deficiency disease but rather a nutritional deficiency in the sense that more factors than vitamin K deficiency alone are *necessary for its production In the absence* of complicating factors however vitamin K therapy results in the relief of all signs of the disease

History Dam and his associates in Copenhagen *produced a disease in chicks by feeding them a diet* washed in ether and observed that a widely distributed antihemorrhagic substance was curative Dam proposed a term vitamin K for this Quick in America then suggested that a deficiency of vitamin K was present in patients who had obstructive jaundice Butt and his associates showed that such patients had a deficiency of prothrombin Maccorquodale McKee Doisy Almquist Klose Fieser and many other investigators made possible the final isolation and synthesis of vitamin K

A number of compounds have been tested for vitamin K activity and many have been found active the two most important at the present time are vitamin K_1 and vitamin K These are fat soluble and at low temperatures form yellow crystals

Etiology Because of its relationship to prothrombin vitamin K appears to be necessary for normal physiological function of the liver and for blood coagulation

In man an inadequate intake of vitamin K is seldom if ever responsible for prothrombin deficiency *The vitamin is widely* distributed in chlorophyll-containing plants such as green leaves alfalfa spinach and cabbage As it is fat soluble it is not absorbed from the upper intestine unless conditions are favorable for the absorption of fat An intact hepatic parenchyma is essential if vitamin K is *to enter into prothrom*bin formation The vitamin is said to be stored in only small amounts in the body Many chronically debilitated persons have moderate hypoprothrombinemia which apparently is not directly attributable to primary vitamin K deficiency

Diagnosis Blood coagulation time and *bleeding time have been found unsatisfac*tory indices of the potential danger of hemorrhage because abnormal values do not appear until hemorrhage is imminent The measurement of the prothrombin concentration or prothrombin clotting time is a more accurate measure of the tendency to bleed

The decrease in concentration of prothrombin is a phenomenon in which numerous factors are involved Bleeding because of prothrombin deficiency may be anticipated in any disease state which results in inadequate intestinal absorption or hepatic utilization of vitamin K Hemorrhage may result when bile is excluded from the gastrointestinal tract by obstruc*tion due to pancreatic neoplasm postopera*tive structure of the common duct intermittent obstruction by stones or hepatic injury from chronic cholecystic disease or hepatotoxins The bleeding may manifest itself as a slow oozing of blood from the *gums nose or gastrointestinal tract or* more frequently from the incisional site The hemorrhage occurs most frequently on the first to fourth postoperative days but may occur later Severe melena or hematemesis may occur though uncommonly and may even be uncontrollable with repeated transfusions Invariably a prolonged prothrombin clotting time will be found A multiplicity of factors may produce this situation loss of blood trauma anesthesia *an already depleted prothrombin and ex*cessive administration of Dicumarol or its derivatives which act as a vitamin K antagonist

Hemorrhage in patients with various intestinal disorders such as sprue celiac disease chronic ulcerative colitis intestinal obstruction with intubation external biliary fistulas ileac stomas with profuse discharge short-circuiting operations and ileitis should lead the physician to suspect *prothrombin deficiency In such conditions* it is of utmost importance to follow the prothrombin level A special problem is encountered in infants who manifest a deficiency of prothrombin at birth This is attributed to the absence from the intestinal tract of bacterial flora which have some relationship *to the synthesis* of vitamin K to the limited absorption of fat to the insufficiency of bile and to the usually

hypermotile gut during the first few days of life The deficiency of prothrombin in infants is often spontaneously remedied within three or four days after birth If a surgical procedure is contemplated in the newborn infant one should follow the prothrombin level with particular caution

Treatment In most instances vitamin K_1 or K or related compounds are effective in the prevention and control of bleeding due to a lowered prothrombin level The tendency of a patient to bleed is not always accurately indicated by the prothrombin measurement Thus when prothrombin deficiency is suspected therapy should be instituted before bleeding starts The water soluble preparations (menadione bisulfite) may be given parenterally when intestinal absorption is poor but adequate functioning liver parenchyma is necessary in any circumstance

Minimal requirements for the infant child mother or adult are not known but a dose of 1 to 2 mg per day of menadione usually corrects the deficiency unless there is inadequate absorption or an increased need because of diarrhea or sprue The development of untoward reactions from the oral or parenteral administration of preparations of vitamin K need not be feared Amounts far above the therapeutic dose have been given to adults (50 mg orally 10 mg intravenously) without the appearance of any signs of toxicity The oral administration of larger amounts (180 mg of menadione) to human beings has been followed by vomiting and porphyrinuria

Bleeding may occur with little warning It is the writer s practice to determine the prothrombin clotting time of every patient with jaundice or other conditions which may lead to hypoprothrombinemia and to administer vitamin K (2 mg of menadione) with bile salts orally or water soluble synthetic progenitors (menadione bisulfite 4 8 mg) parenterally if the prothrombin clotting time is prolonged One to 2 mg of a synthetic compound with vitamin K activity together with 1 to 3 gm of bile salts given orally usually suffices This dosage should be repeated as indicated

Preoperative and postoperative care in the jaundiced patient is of utmost importance After an operation the prothrombin clotting time usually increases to some extent for three or four days but may increase rapidly days later In such patients the prothrombin concentration should be determined daily for at least four days and then every other day for another ten days Some think it is best to administer vitamin K regardless of the postoperative prothrombin clotting time

The problem of treating patients who are actively bleeding is difficult The alimentary tract is often filled with blood and the patient frequently is dehydrated and in shock Such cases usually require a transfusion of blood which provides a temporary store of prothrombin for about 8 hours In cases in which severe bleeding into the alimentary tract is associated with low prothrombin 25 mg of a water soluble vitamin K (menadione bisulfite) can be given either orally or parenterally Absorption is more certain when the parenteral route is used

In cases of severe hepatic damage 3 to 5 mg of substances with vitamin K activity should be administered daily even though the prothrombin clotting time response is slight Death from hemorrhagic diathesis rarely occurs when such therapy is applied Should the usual dose be tripled without effect no additional amount will be effective When hepatic damage is severe utilization of vitamin K substances may prove inadequate

The newborn infant may be treated by giving 1 5 mg of menadione at birth which prevents transitory hypoprothrombinemia and hemorrhagic disease Many obstetricians advocate giving vitamin K to the mother 12 to 24 hours before parturition since it has been found that the infant has a higher prothrombin level when the mother has received vitamin K prior to delivery The author prefers to give a pregnant woman 2 mg daily for one week preceding delivery and during labor if necessary

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Mixed Deficiency Diseases

Diets that fail to supply one nutrient in adequate amounts are deficient in others and every method of study has indicated the predominance of mixed rather than single deficiencies Accordingly a person may have a number of diseases simultane

ously although diagnostic evidence of only one may be apparent at the time he is examined by the physician The basis of treatment of all patients with deficiency diseases is a diet that supplies liberal amounts of all the essential nutrients In many instances however food cannot be consumed in sufficiently large amounts to supply the patient with the quantities of nutrients needed to restore him to health Too often it is forgotten that we must treat the patient rather than his disease and that treatment must be adapted to the individual case

In treating the clinical syndromes of beri beri pellagra riboflavin deficiency and scurvy we give a basic formula consisting of 10 mg of thiamine 50 mg of niacin 5 mg of riboflavin 75 mg of ascorbic acid and 5 mg of folic acid When we find that the symptoms of one deficiency disease predominate we add to this formula more of the vitamin specific for the predominating deficiency In beriberi 10 mg of thiamine is added daily in riboflavin deficiency 5 mg of riboflavin twice daily in scurvy 100 mg of ascorbic acid three times a day and in mild pellagra 50 mg of niacin amide three times a day If the pellagra is severe the patient is given 150 mg of niacinamide three times a day in addition to the basic formula When the patient is moribund it may be necessary to resort to parenteral injections in order to prolong and indeed even to save life When large amounts of glucose are injected daily we recommend the inclusion of 20 mg of niacinamide 7 5 mg of riboflavin and 5 mg of thiamine In a few instances we have found it desirable to inject 50 mg of ascorbic acid in physiological solution of sodium chloride

When there is any tendency to bone marrow failure in patients with definite deficiency disease states we proceed to make a precise diagnosis On many occasions it is found that the patients have evidence of nutritional macrocytic anemia or iron deficiency anemia

Deficiency diseases frequently occur in patients with true pernicious anemia or in women who are pregnant thus a group of diseases may be operating simultaneously in the patient who may have physiological stress such as pregnancy or lactation or who may have organic and primary disturbances such as failure of the intrinsic factor of the stomach

The four principles used in treating mixed deficiency diseases are

1 DIET 4000 calories 120 to 150 gm protein rich in vitamins and minerals

2 BASIC THERAPY Thiamine riboflavin niacinamide ascorbic acid orally

3 ADDITIONAL MEDICATION Synthetic vitamins as indicated orally or parenterally

4 NATURAL B COMPLEX Brewers yeast or extract or rice bran extract and/or liver extract orally or parenterally

One of the basic formulas employed is

	Daily
Folic acid	5 mg
Thiamine	10 mg
Niacinamide	150 mg
Riboflavin	10 mg
Ascorbic acid	150 mg
Vitamin B_1 and Activator *	10 mcg vitamin B_{12}

* Equivalent to 10 micrograms of vitamin B_{12} and intrinsic factor adequate to form its conjugate

TOM D SPIES

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Sprue and Allied Malabsorption Syndromes

(Tropical Sprue Nontropical Sprue Idiopathic Steatorrhea)

Definition Sprue is a chronic disease of unknown etiology without specific gross anatomicopathological changes in which absorption from and motility of the small intestine are impaired The outstanding clinical features of the disease are the signs and symptoms of abnormal intestinal function and manifestations of associated nutritional deficiency states Primary (or idiopathic) sprue is to be distinguished from sprue syndromes secondary to diseases with specific pathological lesions which impair function of the small bowel such as regional enteritis Whipple s disease tumors of the small intestine resections or anastomoses

Although long considered to be a disease limited to tropical and subtropical climates

sprue has been recognized among patients in the temperate zones of Europe and North America with increasing frequency during the past half century Many students of the disease agree that tropical and non tropical sprue (idiopathic steatorrhea) in adults and celiac disease in infants and children are manifestations of the same underlying disease state

History The term sprue apparently derives from the Dutch word Sprouw meaning aphthous stomatitis which was first used by Katelaer in 1669 to designate an illness characterized by sore mouth and voluminous stools The first description of sprue in 1766 is credited to an Englishman William Hillary in the Barbados but it was not until 1880 that the publications of Sir Patrick Manson in China and Van der Burg in Batavia clearly identified sprue and awakened widespread scientific interest in the disease The extensive studies of Thaysen in 1932 led to more frequent recognition of sprue in temperate climates and pointed to the underlying identity of tropical sprue nontropical sprue and celiac disease

Etiological Factors The cause of sprue remains unknown Among many theories the concept that the disease is caused by nutritional deficiency has probably received the widest support Although severe deficiency states often exist in patients with sprue it has not been possible to prove that they constitute the underlying cause of the disease since they may well be secondary to pre existing impairment of absorption from the small bowel from other causes Evidences favoring sprue as a primary deficiency state are (1) the frequency with which an inadequate dietary intake particularly of proteins precedes the onset of symptoms of sprue in tropical climates (2) the favorable response to treatment with diets adequate in proteins calories minerals and vitamins (3) the favorable response of many patients to treatment with liver extract vitamin B_1 or folic acid Evidences which indicate that sprue is not caused primarily by nutritional deficiencies are the fact that the disease develops among many patients either in tropical or temperate climates who have always eaten a very adequate diet and the fact that correction of deficiencies in patients with sprue does not restore intestinal function to normal Although clinical and hematological responses of such patients to treatment may be satisfactory careful study during remissions usually reveals evidence of impaired intestinal function and clinical relapses are not uncommon in spite of adequate treatment

The idea that infection is a primary cause of sprue has been largely abandoned because of the failure to identify an infecting organism and the absence of fever leukocytosis or anatomicopathological evidence of inflammation in most cases The fact that some patients seem to respond favorably to treatment with sulfonamides and antibiotics suggests that infection may play a contributory role Allergy to wheat and rye glutens has been implicated as an etiological factor in celiac disease and in some cases of nontropical sprue It is possible that sensitivity to other food proteins may be of importance As yet the role of allergy as an etiological factor of sprue is incompletely understood

Constitutional and inherited factors probably are important The occurrence of the disease in more than one member of the same family is not uncommon and apparently also a racial predisposition exists—light skinned people reportedly being more susceptible than dark skinned people It is possible that patients with sprue inherit a functional defect of the gastrointestinal tract which may not become evident until precipitating factors such as infection dietary deficiency pregnancy allergy or other unknown influences bring it to light In order to produce the clinical symptoms of sprue such extrinsic factors would necessarily be of greater severity and importance in patients with mild constitutional defects than in those with severe defects This hypothesis might explain the high incidence of sprue in the tropics where dietary deficiency and infection are relatively common Also it might explain the better response to treatment of most patients with tropical sprue as compared with those with the nontropical variety since in tropical sprue reversible extrinsic factors would more often and to a greater degree be responsible for the production of clinical symptoms

Incidence and Epidemiology Sprue is endemic in certain countries of the Far East including India Ceylon Indo China the Malayan archipelago the East Indies the Philippine Islands China Korea and Formosa It occurs in the West Indies but apparently is rarely observed in Africa The greatest reported incidence of sprue is among Europeans who have resided in the tropics for long periods However this may be due to the fact that the disease often is not recognized in native populations Although the disease is less common in temperate climates than in many areas of the

tropics it cannot be considered a rarity in Northern Europe and North America where sizable groups of patients with sprue have been observed in a number of medical centers

The incidence of sprue in Puerto Rico apparently is declining though Suarez reported that more than 500 cases have been encountered there during the past thirty years In India during World War II sprue occurred in epidemic form and became an important cause of morbidity among English and Indian troops and Italian prisoners of war The epidemics occurred in a seasonal manner but the season varied with different geographical areas and the outbreaks could not be satisfactorily explained on the basis of any single etiological factor However dietary deficiencies were considered to be of importance particularly among Italian prisoners and Indian troops

The sex incidence of the disease has varied in different published series Reports concerning the incidence of sprue among British residents in tropical climates have reflected a preponderance of males On the other hand females have outnumbered males in series reported from Puerto Rico and New York City while British reports concerning nontropical sprue have indicated that the incidence of the disease is approximately equal in the two sexes

Sprue may begin at any time of life though the onset of symptoms is most likely to occur between the ages of twenty five and fifty five years In the tropics the disease rarely begins before the age of ten or after the age of seventy In many patients with nontropical sprue the onset can be traced back to the occurrence of celiac disease in childhood

Morbid Anatomy Necropsy has shown depleted stores of fat and atrophy of the tongue and internal organs but has not disclosed lesions in the intestines or elsewhere considered to be specific for sprue Shortening and blunting of the villi in the small intestine (not attributable to post mortem changes) were noted in some cases Recently more significance has been attached to the microscopic findings in mucosal biopsies of the small intestine removed at operation or by means of an intestinal intubation technique Such studies have revealed mucosal atrophy and blunting flattening and reduction in size of the villi with consequent reduction in the total absorbing surface of the small intestine

Pathological Physiology and Chemistry All of the clinical and metabolic disturbances encountered in patients with sprue can reasonably be attributed to the impaired intestinal function invariably present in this disease The fact that identical syndromes are produced by extensive resections of the small intestine and diseases that interfere with its function (anastomoses tumors inflammation) is strong evidence in favor of such an explanation Nevertheless the possibility remains that some manifestations of sprue are due to other primary metabolic abnormalities as yet unidentified

Studies of patients with nontropical sprue have shown impaired absorption of all nutrients including fat protein carbohydrates vitamins minerals and even water Although steatorrhea is the most easily recognized and characteristic feature of this disease the fecal content of nutrients other than fat also is increased Such abnormal fecal losses usually associated with diarrhea and often with inadequate dietary intake result in loss of weight and the development of hypoproteinemia anemia osteomalacia and hypokalemia as well as other evidences of deficiency states including those of minerals and all the water soluble and fat soluble vitamins Fecal losses of fat may be many times the normal value and the quantity of fecal nitrogen may also be considerably increased The anemia of sprue can be attributed to the deficiency of essential hematopoietic substances (vitamin B_1 folic acid iron and protein) malabsorption of which has been demonstrated in this disease Multiple deficiencies of these substances may account for the not infrequent failure of any one of them administered therapeutically to correct the anemia completely Vitamin B deficiency is indicated by glossitis stomatitis cheilosis and rarely by the appearance of peripheral neuritis Other deficiencies of considerable clinical importance are those of vitamin D and calcium which may produce osteomalacia and tetany of vitamin K with its associated hemorrhagic tendency and of potassium which can produce weakness apathy mental disturbances and even coma and death in this disease Tests for the absorption of glucose vitamin A and carotene have some use in the diagnosis of sprue and other malabsorption diseases

Roentgenologic studies of the small bowel disclose the so called deficiency pattern with hypomotility and alterations in

mucosal relief especially of the jejunum The small bowel is dilated the mucosal markings are thickened the contour of the lumen is smooth the usual markings of the valvulae conniventes are obliterated barium is clumped in elongated masses and after the bulk of the opaque meal has passed remnants of the barium adhere to the walls giving them a peculiar flecked appearance There is evidence of hypersecretion or retention of fluid in the small bowel These changes become less marked during remissions of the disease but seldom disappear entirely

Symptoms and Findings Diarrhea weakness and loss of weight are prominent symptoms in sprue The onset of the disease may be insidious with episodes of loose stools and asthenia which may recur at irregular intervals for many years without becoming sufficiently bothersome to cause the patient to seek medical advice In other instances the onset may be more abrupt and even explosive in nature Diarrhea often occurs in attacks lasting a few days to several weeks or longer and as the disease progresses this symptom may become continuous During diarrheal episodes stools are characteristically nonbloody soft bulky frothy greasy and light colored but often they may be watery and without gross evidence of steatorrhea even when excessive fat is present The number of stools varies but it is seldom greater than fifteen in one day Nocturnal movement of the bowels is common and incontinence of feces may occur Between spells of diarrhea the stools may appear normal in color and consistency In rare instances diarrhea may be absent and the patient may even complain of constipation

Anorexia weakness and loss of weight may be severe Loss of 25 pounds or more is common and in extreme cases the patient may lose a third to a half of his customary body weight A few patients complain of failure to gain weight in spite of an excessive appetite and a large intake of food Glossitis and stomatitis are frequent symptoms and may cause sufficient pain to interfere with alimentation Most patients complain of abdominal discomfort particularly flatulence and distention However severe and persistent abdominal pain is uncommon and usually indicates the presence of complications or another disease Hypocalcemic tetany or skeletal pains associated with osteomalacia are the presenting complaints of a few patients with nontropical sprue but rarely occur in the tropics where exposure to sunlight apparently prevents the development of vitamin D deficiency

On physical examination emaciation and dehydration pallor of the skin and mucous membranes and aphthous stomatitis or glossitis with or without patchy atrophy of the tongue are frequently seen but the most striking feature is the distended protruding tympanitic abdomen The blood pressure is low and fever is absent except in the presence of intercurrent infection Edema of the lower extremities is common In well developed sprue generalized brownish yellow pigmentation suggestive of that seen in Addison s disease may occur or the pigmentation may affect mainly the exposed surfaces of the skin The liver and spleen usually are not palpable Although the deep tendon reflexes may occasionally be absent severe peripheral neuritis and subacute combined degeneration of the spinal cord rarely are encountered Chvostek s and Trousseau s signs may be positive or manifestations of tetany may be present Clubbing of the fingers can occur if the disease is of long standing and hemorrhagic tendencies such as petechiae ecchymosis and bleeding from the orifices are sometimes observed

Demonstration of the presence of steatorrhea is essential to the diagnosis of sprue Steatorrhea may be suspected from gross or microscopic inspection of stool but the most reliable method of proving its presence and measuring its degree is by intake excretion studies Feces collected over a period of three to six days while the patient is eating a diet containing a moderate amount of fat (70 to 100 gm daily) is analyzed for total quantity of fat Under the circumstances an excretion of more than 10 gm per day establishes the presence of steatorrhea Measurements of the percentage of fat in the dry weight of single specimens or of mixed collections of feces may give falsely normal values even though excessive quantities of fat are present if (as frequently happens) the quantity of nonfatty solid constituents of the feces also is increased Further evidence of malabsorption is obtained when curves showing results of glucose or vitamin A tolerance tests are flat and the concentration of carotene in the serum is below the normal range An increased prothrombin time resulting from impaired absorption of vitamin K is likewise of diagnostic value Appropriate chemical analyses of the blood serum or plasma often will give evidence

of one or more deficiency states with low values for proteins calcium phosphate sodium chloride or potassium The hemogram and stained smears of the blood may be normal but more frequently they reveal anemia This is usually macrocytic in type but may be normocytic and hypochromic Macrocytosis either with or without anemia occurs at some time in the course of almost all cases of sprue though it may not be continuously present In some patients the peripheral blood picture is indistinguishable from that of pernicious anemia and is associated with megaloblastic bone marrow The incidence of megaloblastic anemia among reported cases of tropical sprue is considerably higher than that among those with nontropical sprue probably because this type of anemia has frequently been used as a diagnostic criterion for sprue in the tropics whereas in temperate climates more diagnostic emphasis has been placed on the presence of steatorrhea

Roentgenologic studies of the small intestine may be of considerable diagnostic value in revealing the aforementioned "deficiency pattern and in ruling out such lesions of the small intestine as enteritis and tumors which can produce a clinical picture closely simulating that of sprue Although suggestive of sprue the so called deficiency pattern is by no means pathognomonic of this disease since similar findings have been described in a variety of clinical states Roentgenographic studies of bone may show evidence of impaired calcification and pseudofractures characteristic of osteomalacia

Diagnosis The diagnosis of sprue depends on the demonstration of intestinal malabsorption (steatorrhea) and the deficiency states of foodstuffs minerals and vitamins associated with it Exclusion of pathologically recognizable entities capable of producing the same syndrome is also necessary The diagnosis presents few difficulties in well established cases in which a fatty diarrhea flatulent indigestion glossitis anemia tetany a protuberant distended abdomen vitamin deficiencies loss of weight and muscular wasting are present particularly when symptoms have been present for several years with remissions and exacerbations However milder cases without grossly evident steatorrhea or severe anemia are frequently overlooked

Establishment of the existence of steatorrhea eliminates pernicious anemia tropical macrocytic anemia pellagra and other non steatorrheal diseases which may closely resemble sprue in some respects The finding of free gastric acid after histamine stimulation (present in approximately 80 per cent of patients with sprue) and the failure to absorb radiochromium marked vitamin B_1 when intrinsic factor is simultaneously administered also serve to differentiate sprue from pernicious anemia Pancreatic steatorrhea when due to chronic pancreatitis can almost always be identified by a history of recurrent severe abdominal pain diabetes or roentgenographic evidence of calcification in the pancreas and when due to carcinoma of the pancreas by the presence of jaundice or a progressive downhill course Roentgenologic examination of the small intestine helps to rule out regional enteritis and tumors of the small bowel though at times the latter can be recognized only by surgical exploration Biopsy of the small intestine or mesenteric lymph nodes is necessary to establish an unequivocal diagnosis of Whipple s disease though this may be suspected when the sprue syndrome occurs in a white man with a history of arthritis fever abdominal pain and a downhill course

Prognosis The course of sprue is characterized by remissions and exacerbations which make difficult the evaluation of any particular therapeutic measure In general however the symptoms tend to progress until treatment is instituted A large majority of patients respond satisfactorily to treatment particularly those with severe deficiency states Remissions are often maintained as long as therapeutic measures are continued but relatively few patients are cured in the sense that they can permanently dispense with all therapeutic precautions Critical study of patients who have made a complete clinical and hematological recovery from either tropical or nontropical sprue usually reveals evidence of impaired function of the small intestine (malabsorption abnormal motility) Few carefully conducted intake excretion studies of such patients have been carried out but of those reported most show a return toward normal rather than full attainment of a normal state Remissions from sprue are often incomplete and relapses may occur even during periods of adequate treatment or sometimes years after an initial episode of the disease

Many patients under treatment for sprue may live many years in a satisfactory state of health Others experience periodic recurrences which may become progressively more resistant to therapy while a few may be resistant from the beginning of treatment Death may be due to a variety of

causes including cachexia infection hemorrhage (hypoprothrombinemia) and potassium deficiency

Prevention and Treatment Since the cause of sprue is unknown there is no completely satisfactory method of prevention Avoidance of residence in those areas of the tropics where the disease is common and ingestion of a well balanced diet rich in animal protein should be of prophylactic value

In the treatment of the disease complete dependence should not be placed on any single therapeutic measure but rather a program of treatment designed to avoid irritating or overburdening the malfunctioning bowel and to correct the deficiency states should be followed Physical and emotional rest including rest in bed are helpful in establishing remissions Dietotherapy is of fundamental importance Because fat causes abdominal discomfort and diarrhea the amount of it in the diet is restricted to 50 to 70 gm per day The diet is rich in calories vitamins and proteins (particularly those of high biological value) and is composed of foods that leave only a moderate amount of residue A large proportion of the carbohydrates are those from fruits and simple sugars Recently a diet free of wheat and rye gluten first used successfully in the treatment of celiac disease has been found efficacious in the treatment of some patients with nontropical sprue

Liver extract vitamin B_1 and folic acid have all been recommended as specific treatment for sprue and impressive clinical and hematological remissions have resulted from their use particularly in patients with tropical sprue with megaloblastic anemia However maximal benefits from these hematopoietic agents are usually obtained only when dietary treatment is simultaneously administered and the remissions they produce are not always complete They have no demonstrable effect on the steatorrhea of nontropical sprue and have not been shown to correct completely the absorptive defect in the tropical variety The administration of one of them however is always indicated in the presence of macrocytic anemia and perhaps may be of value also in nonanemic patients who do not respond to dietary treatment alone Some patients with macrocytic anemia will respond to one of these agents after being found resistant to another Dosage should be individualized Concentrated liver extract is given intramuscularly in doses of 1 0 ml each day for three days then 1 0 ml twice weekly for three months and then a maintenance dose of 1 0 ml weekly Vitamin B_1 also is administered parenterally according to a similar time schedule in doses of 15 micrograms Folic acid may be administered either orally or parenterally The usual dose is 15 to 20 mg per day for two weeks then 10 or 15 mg daily until complete symptomatic and hematological remission have been attained The maintenance dose is 2 5 to 5 0 mg per day Folic acid is contraindicated in patients with neurological involvement

Deficiencies of other vitamins and minerals are corrected as necessary Each patient should receive at least one multiple vitamin capsule daily and if evidence of vitamin deficiencies exists large additional doses of the several vitamins may be given Water soluble preparations having vitamin K activity given orally in doses of 4 mg daily will usually correct a hemorrhagic tendency and return the prothrombin time to normal The vitamin B complex may be given in large doses to patients with peripheral nerve lesions and glossitis Vitamin D in daily doses of 50 000 to 400 000 I U orally may be given in the treatment of osteomalacia and tetany To such patients calcium is administered orally in the form of calcium lactate 1 to 4 drams three times a day depending on the severity of the condition Potassium deficiency is corrected by the oral or parenteral administration of potassium salts Patients with iron-deficiency anemia may require parenteral administration of iron because oral preparations are poorly tolerated and poorly absorbed Blood transfusions are sometimes helpful in controlling intractable anemia and severe hypoproteinemia

Cortisone hydrocortisone prednisone prednisolone and corticotropin are useful as a supplementary treatment in patients who do not respond satisfactorily to the usual measures The object in their use is to establish a remission and then gradually withdraw the medication entirely Thus the patient is spared the dependency on steroids and the troublesome and sometimes dangerous side-effects which result when high level dosages are maintained over long periods as well as the relapses which often occur when such treatment is discontinued The starting daily dose of cortisone is generally 100 mg given orally in four doses of 25 mg each After one to three weeks the time depending on the clinical response the total daily dose is gradually reduced over one to four months and finally discontinued if relapse does not

occur Repeated courses may be adminis tered for exacerbations of the disease

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Diseases of Metabolism

Inborn Errors of Metabolism

INTRODUCTION

In 1908 A E Garrod pointed out that not only gross anatomical malformations but also more subtle metabolic defects may be genetically determined citing as examples albinism alkaptonuria cystinuria and pentosuria This concept of inborn errors of metabolism has proved to be extraordinarily fruitful It is now apparent that any segment of the total of metabolic processes—protein carbohydrate lipid nucleic acid electrolyte porphyrin or pigment metabolism—may be subject to distortion as the result of an inborn metabolic error Thus in this category fall such diverse disorders as the hemophilias congenital agammaglobulinemia the hemoglobinopathies certain hemolytic anemias Gilbert s disease congenital methemoglobinemia the porphyrias a variety of renal tubular defects cystinosis oxalosis Wilson s disease primary gout phenylketonuria a variety of connective tissue defects the lipidoses essential hypercholesterolemia and hyperlipemia several forms of sporadic familial cretinism hypophosphatasia galactosemia glycogen storage disease familial periodic paralysis some of the progressive muscle dystrophies and myotonias and many others More doubtless remain to be uncovered

The fault in inborn errors of metabolism apparently lies in the genetic deoxyribonucleic acid template from which enzymes and other proteins are generated The resulting metabolic defect may be complete or partial The functional deficiency may have profound clinical consequences if a critical activity is wholly blocked particularly if adaptive alternative pathways are inadequate or it may not be clinically overt especially in the heterozygote The anomaly may be apparent at birth or not until later in life (if at all) and then sometimes only if made manifest by environmental stresses

The metabolic block resulting from innate lack of a critical enzyme may become evident as absence of the end product of the affected reaction—for example melanin in albinism—or by abnormal accumulation of the substrate To illustrate the latter instance in galactosemia there is a deficiency of galactose 1 phosphate uridyl transferase an enzyme necessary for the conversion of galactose 1 phosphate to glucose 1 phosphate thus leading to accumulation of galactose 1 phosphate (and galactose) in the blood and tissues Any one of several enzymes necessary to complete a particular sequence of metabolic reactions may be missing A multiple pathogenesis of this kind has been established for glycogen storage disease which may result from any one of three distinct inborn errors lack of glucose 6 phosphatase lack of "branching" enzyme necessary for normal glycogen synthesis or lack of "debranching enzyme required for glycogen degradation

Some inborn deficiencies of metabolism become clinically manifest only with time and the complex interplay of diet endocrine function renal function infection or other intercurrent disease emotional stress and other poorly understood factors The delay in appearance of a clinical deficit may be due to gradual storage of a metabolite The principal clinical manifestations may be determined by secondary complications of the primary defect as in the slow cumulative deposition of copper in selective areas of the brain liver and kidney in Wilson s disease

An interesting group of latent inborn errors of metabolism has been uncovered

as a result of study of the mechanisms of drug hypersensitivity Sensitivity to prima quine and to the fava bean has been shown to be related to defective erythrocyte glu cose 6 phosphate dehydrogenase Untoward reactions to succinylcholine have been ascribed to inadequate pseudocholinesterase activity Indeed as Haldane has pointed out it may be with the study of diatheses and idiosyncrasies differences of innate *make up which do not necessarily lead to* disease but may do so that future in vestigation in this field will be largely concerned

The diversity of the clinical manifesta tions of the inborn errors of metabolism in part reflects the diversity of the special ized tissue functions which may preferen tially be impaired Thus the absence of a specific enzyme may particularly affect a function of the liver (homogentisic acid oxidase deficiency in alkaptonuria to cite one of many examples) bone (alkaline phosphatase deficiency in hypophospha tasia) red cells (a deficiency in erythro cyte glycolysis in hereditary spherocytosis) thyroid (a deficiency in the coupling of iodotyrosines in one form of sporadic famil ial cretinism) muscle (defective potas sium utilization in periodic paralysis)

A number of inborn errors of metabolism are expressed principally or wholly by one or another deficiency in renal tubular func tion not infrequently occurring in a variety of combinations For the most part these anomalies are characterized by defects in tubular reabsorption and presumably re flect deficiencies in enzyme components of transport systems resident chiefly in the proximal convolution The increased renal clearance—whether of amino acids hex oses pentoses phosphate calcium potas sium bicarbonate water—is associated with low or low normal concentrations of the plasma component(s) in question in contrast to those extrarenal metabolic dis orders in which excessive urinary excre tion is due to overflow of an accumulation of some metabolite in the circulating fluids The depletion which results from failure of renal conservation may of itself have untoward effects as in the development of rickets or osteomalacia in renal hypo phosphatemia or muscle weakness follow ing excessive urinary loss of potassium In some instances the chief hazard is renal calculus formation when a constituent of low solubility is excreted in excess (cystin uria oxaluria idiopathic hypercalcinuria) In the case of renal tubular acidosis the tendency to calcium phosphate deposition as nephrocalcinosis or nephrolithiasis is favored by excessive urinary excretion of phosphate and calcium and is further facili tated by the accompanying defect in acidi fication of the urine

Inborn errors of metabolism may affect the biosynthesis of proteins other than en zymes Marfan s syndrome and the Ehlers Danlos syndrome are examples of genet *ically derived deficiencies of specific struc* tural elements of connective tissue The genetically determined defects in the syn thesis of the heme carrier protein globin abnormalities which are responsible for the various hemoglobinopathies have been par ticularly well studied Ingram has shown that hemoglobins S and C differ from hemo globin A only in the substitution of a single amino acid valine or lysine respectively for glutamic acid at just one point in the long chain of amino acid sequences which constitute the globin molecule As a con sequence of these minute variations in composition the surface charges of the hemoglobin S and C molecules are altered sufficiently to permit separation from hemo globin A by electrophoresis The solitary defect in the globin moiety of hemoglobin S presumably is responsible also for the abnormal aggregation of hemoglobin S molecules within the red cells when oxy gen is lost (sickling) and its far reaching clinical consequences Similar minor changes in the composition of proteins pos sessing enzymatic properties might account for their apparent absence in inborn errors characterized by one or another metabolic block

The study of the pathogenesis of inborn errors of metabolism has elucidated many pathways of normal as well as abnormal intermediary metabolism and will undoubt edly continue to be a rewarding area of investigation Moreover such studies have thrown new light upon the basic aspects of the relationship of the deoxyribonucleic acids of the genes to the enzymic constitu tion of cells Better insight into the nature of these disorders has made it possible further to initiate plans of therapy some of which have proved more effective than might have been supposed It is not to be sure at present feasible to replace missing intracellular enzymes but the effects of deficiencies can be circumvented in some instances whether by dietary regulation (galactosemia phenylketonuria essential hyperlipemia for example) drugs (con genital methemoglobinemia gout Wilson s

disease) or simple replacement of depleted electrolytes or metabolites (as in a variety of renal tubular deficiencies)

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CONGENITAL METHEMOGLOBINEMIA

Definition Congenital methemoglobinemia is characterized by abnormal accumulation of methemoglobin in the blood as a consequence of an inherent inability to reduce the ferric iron of methemoglobin which is incapable of oxygenation to the ferrous iron of hemoglobin In severe cases methemoglobin may comprise 30 per cent or more of the total pigment (normally less than 1 per cent) thus resulting in hypoxemia due to inadequate transport and *availability of oxygen*

Etiology There is no history of exposure to the various chemical agents responsible for acquired methemoglobinemia (see p 505) However since the red blood cells of the newborn normally do not yet contain their full quota of the enzyme system required for reduction of methemoglobin to hemoglobin the infant is peculiarly vulnerable to such agents

There are at least two separate forms of congenital methemoglobinemia due to different inborn errors which block reduction of methemoglobin by distinct metabolic pathways In one group of cases there appears to be according to Gibson a specific deficiency in erythrocyte coenzyme factor I (diaphorase a flavoprotein) which is necessary for the enzymatic conversion of methemoglobin to hemoglobin occurring normally in the red blood cells This process catalyzed by methemoglobin reductase depends upon the proper utilization of glucose or lactate and requires a sufficient supply of reduced diphosphopyridine nucleotide (DPN H) Another group of cases first differentiated by Horlein and Weber is characterized according to Gerald and others by the presence of methemoglobin M This is an abnormal methemoglobin with distinct spectral characteristics associated with the presence of abnormal hemoglobin M

The trait is generally believed to be transmitted as a recessive in the first group of cases and probably as a dominant in the second The differences in globins may also explain discrepancies in the effect of methemoglobinemia on the oxyhemoglobin dissociation curve which is shifted to the left in some (but not all) cases thus adversely affecting release of oxygen from oxyhemoglobin as well as the oxygen *capacity*

Symptoms and Signs If the defect is sufficiently pronounced congenital methemoglobinemia may be manifest at birth or early in life as a diffuse persistent gray or slate blue cyanosis The contrast between the deep cyanosis at rest and the absence of signs or symptoms of cardiac or respiratory abnormalities should suggest the diagnosis particularly when a familial incidence can be established Exertion however often elicits fatigability dizziness dyspnea tachycardia and severe headache Clubbing of the fingers does not occur In severe cases compensatory polycythemia develops with injection of the conjunctivas engorgement of the retinal veins and *other typical manifestations*

The venous blood is brown and fails to recover its normal color after prolonged shaking in air The oxygen capacity of arterial blood is reduced despite a high hematocrit the oxygen content is proportionately low Spectroscopic examination reveals the presence of excessive amounts of methemoglobin with an absorption band at 630 μ but this is not observed in the case of methemoglobin M

Treatment Recognition of congenital methemoglobinemia is important because confusion with surgically amenable congenital heart disease may lead to needless exploration and because effective treatment is available once the proper diagnosis has been established Continued administration of methylene blue by mouth will restore the oxygen capacity of the blood and maintain the patient free of cyanosis headache and associated symptoms Eder and his co-workers found that daily doses of 240 mg in enteric-coated tablets alleviated all signs and symptoms including polycythemia and reticulocytosis *and were well tolerated* Excessive amounts should not be used because methylene blue in massive dosage causes methemoglobin formation Ascorbic acid in daily oral doses of 300 to 500 mg is also efficacious probably exerting a direct reducing action on methemoglobin

The prognosis as to life is good

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THE GLYCOGEN STORAGE DISEASES

(*Glycogenosis von Gierke s Disease*)

Definition Glycogen storage disease is a composite term referring to a group of distinct inborn errors of carbohydrate metabolism characterized by excessive deposition of glycogen in tissues usually associated with an anomaly of one or another enzyme system concerned with glycogen degradation or synthesis In the hepatorenal form *von Gierke s disease* glycogen storage occurs chiefly in the liver and kidney In *generalized glycogenosis* the distribution of excessive glycogen is more diffuse but is preponderantly in cardiac and skeletal muscle this rare disorder is often referred to as the cardiac form of glycogen storage disease A possibly related form of glycogen disease a myopathy due to inability of the skeletal musculature to utilize muscle glycogen properly has been described by McArdle as another probable inborn error of carbohydrate metabolism (*McArdle syndrome*)

Etiology Cori has shown that in most cases of the hepatorenal type the excessive liver glycogen is of normal molecular structure but there is a deficiency of the liver enzyme glucose 6 phosphatase Hence glycogen can be formed from glucose but glucose 6 phosphate derived from liver glycogen or from ingested glucose through the action of hexokinase cannot be broken down again to regenerate glucose when required In occasional cases of von Gierke s disease there is no deficiency of glucose 6 phosphatase but the metabolic error appears to be a lack of branching enzyme (1 4→ 1 6 transglucosidase) or of debranching enzyme (amylo 1 6 glucosidase) These deficiencies are associated with abnormal molecular structure of glycogen and inadequate utilization for glucose formation because of inaccessibility of the major part of the glycogen molecule to the action of phosphorylase In generalized glycogenosis the metabolic error has not yet been identified—there appears to be neither abnormal glycogen synthesis nor an absence of specific glucose 6 phosphatase In the McArdle syndrome there would seem to be a deficiency of 1 3 diphosphoglyceraldehyde dehydrogenase in skeletal muscle

Symptoms and Signs Von Gierke s disease usually becomes manifest in infancy or early childhood as a problem in feeding or because of undue prominence of the abdomen or delayed growth The most characteristic physical finding usually present in infancy is marked hepatomegaly due to the excessive deposits of glycogen often associated with a considerable increase in neutral fat Jaundice may appear The spleen ordinarily is not enlarged

Because of the limited availability of glucose upon demand hypoglycemia and ketosis develop particularly in the fasting state The symptoms of hypoglycemia may dominate the picture shock or generalized convulsions occurring typically in the early morning hours The realization that frequent feedings allay these symptoms may later result in obesity There is usually delay in growth and development of afflicted children

Generalized glycogenosis is characterized by very marked globular enlargement of the heart in infants with progressive and refractory cardiac failure leading to death in the early weeks or months of life This is due to massive glycogen infiltration of the ventricular musculature giving a lacework appearance to the myocardium There is associated cyanosis dyspnea and malnutrition Macroglossia due to glycogen storage in the musculature of the tongue may be striking Glycogen storage in the renal tubules may be associated with generalized aminoaciduria and other reabsorptive defects

In the *McArdle syndrome* no abnormality is apparent other than a myopathy characterized by pain stiffness and weakness with prolonged contracture of the skeletal muscles upon moderate exercise There is no demonstrable disability of the muscles at rest

Diagnosis Liver puncture biopsy offers the most direct method of diagnosis in the hepatorenal form of glycogen storage disease The liver cells engorged with glycogen present a characteristic plant cell appearance and give the typical staining reactions for glycogen a deficiency of glucose 6 phosphatase may be inferred if the glycogen disappears at a normal rate upon incubation with normal liver homoge

nate The presence of excessive neutral fat may lead to confusion with hypertrophic steatosis or fatty liver associated with diabetes mellitus

Von Gierke s disease should be suspected in infants or children who have marked enlargement of the liver hypoglycemia and ketosis or rapid development of these manifestations when food is withheld and subnormal or no response of the blood sugar to injection of epinephrine (due to unavailability of liver glycogen stores) Additional findings are low serum carbon dioxide combining power ketonuria increased serum glycogen delayed rise in blood sugar after glucose tolerance tests and low curves with rapid fall in levulose and galactose tolerance tests Hyperlipemia and hypercholesterolemia may be so marked as to cause diagnostic difficulties

The cardiomegaly of generalized glycogenosis in infants may simulate subendocardial fibroelastosis and multiple rhabdomyomas of the heart the latter usually associated with tuberous sclerosis of the brain Definitive diagnosis can be made only at necropsy by histochemical or chemical demonstration of glycogen in the tissues

Treatment Treatment in the hepatorenal form of glycogen storage disease is directed toward improvement of nutrition and correction of hypoglycemia and acidosis This is accomplished by frequent feedings including night feedings and the use of glucose or Dexin between meals An extra high protein meal of ground beef and bread late at night has been found helpful Ulstrom et al found corticotropin useful for this purpose Gradual symptomatic improvement as the children grow older is the rule although hepatomegaly usually persists

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GALACTOSEMIA

Definition Galactosemia is an inborn error of metabolism characterized by deficiency of an enzyme galactose 1 phosphate uridyl transferase necessary for formation of glucose 1 phosphate from galactose 1 phosphate in the conversion of galactose to glucose occurring predominantly in the liver In consequence of this metabolic block galactose and galactose 1 phosphate accumulate in the blood and tissues appearing also in excess in the urine after feedings of milk or other foods containing lactose or galactose

Etiology The pattern of inheritance has not been fully elucidated In affected families the trait in some otherwise normal members may be demonstrable only by an abnormal galactose tolerance test and minor discomforts after ingestion of milk

The chief organs of galactose storage are the liver and the spleen Cataracts develop early as in experimental animals fed a high galactose diet Ensuing brain damage may be related to disturbed galactolipid biosynthesis Deposition of galactose in the renal tubules seems to be responsible for the appearance of tubular reabsorptive defects The erythrocytes also are deficient in the transferase and accumulate galactose and galactose 1 phosphate but without obvious ill effects on this account

Signs and Symptoms The infant is normal at birth but soon becomes a feeding problem with vomiting diarrhea and failure to thrive The abdomen is prominent because of distention and increasing hepatomegaly often with jaundice and occasionally with ascites Cirrhosis may develop Mental retardation is a common accompaniment Cataracts appear in more than half of those markedly affected In less severe cases the progress of events is slower a matter of months and mild cases escape with only minor gastrointestinal complaints

Proteinuria is the rule aminoaciduria hyperchloremic acidosis and hypokalemia may develop The pathognomonic feature however is marked galactosemia and galactosuria after ingestion of lactose or galactose Glucose levels in the blood are apt to be reduced and ketosis may occur with vomiting and dehydration

Treatment The key to management is complete exclusion of all milk and other foods containing lactose or galactose Soya milk preparations are frequently employed but may contain polygalactose Holzel and others recommend a milk free diet consisting of eggs sugar margarine and rice flour with appropriate vitamin and mineral supplements If this diet can be instituted early and maintained through the

first three years of life it is possible to prevent the development of liver damage cataract and mental retardation and to effect improvement if these complications are already present

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RENAL GLYCOSURIA

(*"True Renal Diabetes "*)

True renal diabetes is defined as an isolated inborn defect in renal tubular reabsorption of glucose characterized by unremitting urinary excretion of glucose in substantial amounts in association with low or low normal fasting blood sugar and normal glucose tolerance The condition should be differentiated from overflow glycosuria in hyperglycemic states particularly diabetes mellitus alimentary glycosuria due to excessive glucose intake or a lowering of the threshold for glucose within the limits of normal variation and acquired renal glycosuria due to nephrotoxic agents Renal glycosuria may occur in association with other renal tubular defects in a variety of inborn errors of metabolism *and may be acquired as a result of factors which lower the threshold* for glucose

Analysis of clearance data in patients with true renal diabetes indicates considerable variation in the degree of decline in the Tm for glucose In some the evidence suggests heterogeneity of the nephron population in other the nephrons appear to be uniformly defective It is not clear whether this implies a deficiency in some as yet unidentified enzyme system for tubular *transport of glucose*

True renal diabetes is relatively rare It appears very early in life and is compatible with good health and long life showing no predilection for the development of diabetes mellitus No treatment is required

Reference

Taggart J V In Combined Staff Clinic on Disorders of Renal Tubular Function Am J Med 20 448 1956

FRUCTOSURIA

In essential fructosuria an inborn error of metabolism blood fructose levels are excessive and renal tubular reabsorption of fructose is inadequate to remove fructose altogether from the glomerular filtrate *The principal defect may be a deficiency* of fructokinase an enzyme that catalyzes the formation of fructose 1 phosphate from fructose and ATP

After ingestion or intravenous infusion of fructose appreciable amounts may appear in the urine of normal persons ("alimentary fructosuria ") larger quantities in the presence of severe liver damage Because fructose reduces the reagents ordinarily employed in testing urine for sugar fructosuria is often mistaken for glucosuria The disorder involves no disability although a considerable proportion of ingested carbohydrate may be lost from diets rich in fruits or sucrose

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PENTOSURIA

Pentosuria is a rare inborn error of metabolism characterized by excessive excretion of L xylulose a normal pentose metabolite derived from L gulonolactone and ordinarily progressing through D xylulose and the pentose cycle to glucose Essential pentosuria is to be distinguished from alimentary *pentosuria which* may occur in normal persons after the *ingestion* of large amounts of vegetable gums fruits or berries rich in pentosans The condition involves no disabilities but may be confused with glycosuria because of the reducing properties of the pentoses in question The distinction may be made by means of the orcinol reaction lack of fermentation with yeast and preparation of the phenyl osazone derivative

Reference

Peters J P and Van Slyke D D Quantitative Clinical Chemistry 2d ed Baltimore Williams and Wilkins 1946 Vol I p 212

OXALOSIS

Oxalosis is a rare apparently inborn error of metabolism characterized by excessive biosynthesis of oxalic acid which is widely deposited in the tissues as the insoluble calcium salt Renal calculi and

nephrocalcinosis are common manifestations Bone marrow deposits may be extensive causing generalized osteoporosis with typical metaphyseal zones of rarefaction in the long bones Death ensues early in life usually as a result of renal insufficiency

The urinary excretion of calcium oxalate in oxalosis usually is not markedly increased unlike the oxaluria resulting from excessive dietary intake of oxalate or occurring in primary hyperoxaluria

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CYSTINOSIS

(Cystine Storage Disease Lignac s Disease Lignac Fanconi Syndrome)

Cystinosis is an inborn error of cystine metabolism characterized by the deposition of cystine in the tissues particularly in the reticuloendothelial cells of the bone marrow liver spleen and lymph nodes in the cornea (where the crystals can be seen by slit lamp examination thus affording the diagnosis) subcutaneous tissues and kidneys The deposits in the renal tubules are held responsible for the development in infancy of the full blown multiple tubular deficiencies of the Lignac Fanconi syndrome (q v) with accompanying rickets retardation of growth and development dehydration polyuria and eventual glomerular insufficiency Unlike cystinuria the urinary excretion of cystine is not inordinate Bickel has described improvement in the tubular and skeletal defects with administration of large doses of vitamin D in some cases but the prognosis generally is poor In severe cases death is likely to occur in infancy often in uremia

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THE AMINOACIDURIAS

Chromatographic analysis has revealed that the blood plasma normally contains small amounts of more than 20 amino acids in free and conjugated form These amino acids are filterable at the glomerulus but are largely reabsorbed in the tubules appearing in the urine in trace amounts if at all Only 1 to 2 per cent of the total urine nitrogen is made up of urine amino nitrogen chiefly glycine histidine taurine alanine serine asparagine and threonine So limited however is the normal tubular reabsorptive capacity for amino acids that overflow into the urine is apt to occur when there is a substantial rise in the concentration of amino acids in the plasma and consequent augmentation of the filtered load *Overflow aminoaciduria may involve* many amino acids as in hepatic insufficiency with general impairment of urea formation from amino acids Or a single amino acid and its derivatives may appear in excess in the urine as in phenylketonuria In this disorder a specific inborn deficiency of phenylalanine hydroxylase in the liver with resultant block of the conversion of phenylalanine to tyrosine leads to accumulation in the plasma of phenylalanine and its oxidation products phenylpyruvic and phenyllactic acids and all these acids spill over into the urine

Aminoaciduria may occur also as a consequence *of defective tubular reabsorption* of amino acids resulting in excessive rates of clearance with characteristically low or at most normal plasma amino concentrations Such tubular reabsorptive defects may be limited to a single amino acid as in glycinuria or to a selective group of amino acids as in cystinuria or may include a wide variety of amino acids and indeed extend to other metabolites and electrolytes as in the Fanconi syndrome (see p 581) The defects in tubular reabsorption of amino acids may be inborn or acquired They may be acquired in infants with rickets due to vitamin D deficiency (the tubular defects disappearing after treatment with vitamin D) and in vitamin C deficiency Exposure to heavy metals such as lead uranium and cadmium and to other toxic agents such as Lysol and maleic acid may lead to aminoaciduria and associated glycosuria and phosphaturia Tubular reabsorptive defects including aminoaciduria apparently may be acquired as an indirect result of inborn errors of metabolism only secondarily affecting the kidneys for example deposition in the renal tubules of copper in Wilson s disease of glycogen in glycogen storage disease or of cystine in cystinosis Under such circumstances it may be exceedingly difficult to determine whether the aminoaciduria

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is a primary or secondary manifestation of the metabolic error

Cystinuria Of the isolated aminoacidurias due to an inborn error primarily affecting tubular reabsorption that designated cystinuria is characterized in the homozygote by the excessive renal clearance jointly and specifically of four amino acids cystine lysine arginine and ornithine There is no intrinsic block in the intermediary metabolism of cystine nor are tissue deposits of cystine found such as characterize cystinosis (see p 579) The plasma levels of all four amino acids affected are reduced The depletion of these amino acids does not seem to have any deleterious effect and the disorder is compatible with health and long life However the presence in the urine of excessive quantities of cystine which is difficultly soluble at acid or neutral pH favors the formation of cystine calculus and this represents the chief hazard The presence of increased amounts of cystine in the urine can be detected by the cyanide nitroprusside reaction

In prevention and treatment of stone *it is important to encourage a large intake* of fluid during the night also in order to maintain urine volumes copious enough to hold the cystine in solution Alkalinizing agents are of dubious value because the urine ordinarily cannot be made sufficiently alkaline to affect the solubility of cystine significantly The efficacy of dietary restriction of foods rich in methionine and cysteine which are converted to cystine is still under study but it is apparent that the protein intake should be sufficient for growth and/or maintenance

Glycinuria Excessive urinary excretion of glycine occurs in many generalized aminoacidurias but deVries *et al* have called attention to a genetically determined defect specifically of the renal tubular reabsorption of glycine unaccompanied by any other abnormality in renal function The condition is consistent with good health save for a predisposition to renal calculus formation The stone in one case examined proved to be composed almost entirely of calcium oxalate glycine also was present but in very small amount

Another example of an inheritable defect in renal tubular reabsorption limited to a single amino acid is *β aminoisobutyric aciduria* This anomaly seems to have no clinical consequence

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FANCONI SYNDROME

(*de Toni Debré Fanconi Syndrome Lignac Fanconi Syndrome*)

Definition "Fanconi syndrome is an inclusive term used to designate a variable complex of multiple defects in renal tubular function characteristically comprising massive generalized aminociduria renal glycosuria and renal hypophosphatemia Except in late or complicated cases glomerular filtration is little impaired or not at all In the familial type encountered particularly in infants and children the symptom complex includes stunted growth rickets resistant to vitamin D acidosis dehydration and associated cystinosis in some instances The heterogeneous adult type which may be due to inborn errors or acquired is not related to cystinosis and is *apt to be less severe but more inclusive* variously affecting also the renal excretion of water potassium and urate and occasionally overlapping to some extent with renal tubular acidosis When symptomatic the adult form is usually manifested by osteomalacia sometimes by hypokalemic muscle weakness

Etiology Microdissection of nephrons in the Fanconi syndrome by Darmady and co workers has revealed an anomaly of the most proximal segment of the convoluted tubules which is much shortened and joined to the glomerulus by a narrow elongated swan s neck This finding is consistent with renal function studies implicating the proximal convolution as the chief site of the tubular deficiencies It is not clear however whether the swan s neck" anomaly is to be regarded as a primary or secondary cause of the defects in tubular function even in the genetically determined forms of the Fanconi syndrome Bickel s observations in the infantile type associated with cystinosis indicate that the tubular reabsorptive defects are not present at birth but occur subsequently as the tissue deposits of cystine accumulate it is implied that cystine infiltrates into the tubular cells and thus is indirectly responsible for the development of the Fanconi syndrome

The adult form of Fanconi syndrome clearly has a multiple genesis When inborn the disorder is transmitted according

to Dent and Harris as a recessive trait The characteristic tubular reabsorptive defects may however be acquired in part or in whole in a variety of circumstances including exposure to heavy metals such as lead uranium and cadmium or to toxic compounds such as Lysol deposition of copper in the tubules in Wilson s disease of abnormal proteins in multiple myeloma or of carbohydrate in glycogen storage disease and galactosemia in rickets due to vitamin D deficiency and in vitamin C deficiency The etiological relationship in some of these circumstances has been demonstrated by disappearance of the tubular insufficiencies when the primary cause is treated

Symptoms and Signs In the infantile type with cystinosis the children are severely afflicted They are malnourished and dehydrated There is marked polyuria with isosthenuria and excessive thirst Gastrointestinal upsets and muscle weakness are common Resistance to intercurrent infections is impaired Growth and development are delayed the characteristic deformities of low phosphorus rickets relatively resistant to vitamin D are present Progressive glomerular insufficiency is a common late sequel often with termination in uremia In full blown cases survival to puberty is exceptional

The clinical manifestations in the adult are more insidious They are apt to be ushered in and dominated by the manifestations of osteomalacia These include pain in the weight bearing bones difficulty in walking and a waddling gait pathological fractures and sometimes eventual incapacitation Roentgenograms reveal the typical pseudofractures of Milkman s syndrome with symmetrical infractions of bone particularly in the pelvis scapulas femurs humeri and ribs Nephrocalcinosis does not occur renal calculi but rarely In some cases weakness and weight loss are prominent and one must be alert to the development of recurrent episodes of hypokalemic paralyses

The characteristic urinary losses of amino acids glucose phosphate potassium and urate are associated with low or low normal plasma concentrations of these components An increase in serum alkaline phosphatase accompanies the presence of osteomalacia A mild systemic acidosis often is present The urine is apt to be alkaline and occasionally an associated defect in acidification of the urine can be demonstrated

Treatment The response to an alkalinizing regimen often is gratifying Shohl s citrate mixture in doses of 30 ml three times daily usually restores electrolyte balance to this potassium citrate may be added when hypokalemia is pronounced Healing of rickets and osteomalacia requires large doses of vitamin D (50 000 units or more daily) and calcium salts but overdosage (hypercalcemia and its clinical manifestations) should be avoided The outlook in the adult form of Fanconi syndrome is favorable but relapse is the rule if maintenance therapy is discontinued

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RENAL HYPOPHOSPHATEMIA

(Phosphate Diabetes Vitamin D Resistant Rickets)

Definition Renal hypophosphatemia is characterized by a renal tubular defect in reabsorption of phosphate The loss of phosphate in the urine results in a decline in serum inorganic phosphate concentration and a predilection to vitamin D resistant rickets in children osteomalacia in adults

Etiology The isolated tubular defect in reabsorption of phosphate when inborn is transmitted as a dominant according to Winters et al as a sex linked dominant Renal hypophosphatemia occurs also in association with other inborn defects notably renal glycosuria aminoaciduria (Fanconi syndrome) and renal tubular acidosis and may accompany neurofibromatosis Deficient tubular reabsorption of phosphate may also be acquired usually in conjunction with other tubular defects due to renal damage as a complication of an unrelated inborn error of metabolism (Wilson s disease for example) or from exposure to heavy metals in the environment

Signs and Symptoms When the hypophosphatemia is clinically expressed the skeletal manifestations of rickets or osteomalacia (Milkman s syndrome) are usually more pronounced in male carriers of the trait In diagnosis familial incidence de

velopment of the skeletal disorder despite a diet adequate in vitamin D and resistance to vitamin D therapy in ordinarily effective dosage exclude vitamin D deficiency and point to renal hypophosphatemia which can be established by clearance measurements Examination of the urine for glucose and amino acids will determine whether the tubular reabsorptive defect is limited to phosphate or is part of a more diffuse tubular anomaly

Hypophosphatasia causes a disturbance in calcification of cartilage and bone which may simulate the rickets of renal hypophosphatemia This disorder is an inborn error in alkaline phosphatase production in the tissues and is characterized by low serum alkaline phosphatase (in contrast to the increase observed in renal hypophosphatemia with skeletal lesions) normal serum inorganic phosphate hypercalcemia and urinary excretion of phosphorylethanolamine (apparently a natural substrate of alkaline phosphatase) The metabolic error does not appear to involve renal function There is no beneficial response to vitamin D but administration of corticosteroids has been helpful in some cases

Treatment Overt rickets or osteomalacia due to renal hypophosphatemia requires massive doses of vitamin D before a curative action can be obtained The daily therapeutic requirement varies from 50 000 to several hundred thousand or more units and must be determined by the individual response

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RENAL TUBULAR ACIDOSIS

(Renal Hyperchloremic Acidosis)

Definition Renal tubular acidosis is characterized by defective renal tubular function manifested by excretion of inappropriately alkaline or insufficiently acid urine hyperchloremic acidosis hypophosphatemia and intermittent hypokalemia Glomerular filtration is not significantly impaired in uncomplicated cases Renal glycosuria and aminoaciduria characteristically do not occur

Etiology The basic functional abnormality appears to reside in the impaired capacity of the kidney to acidify the urine from this most of the other manifestations of the disorder can reasonably be derived The precise nature of the primary urinary defect in acidification however is still in doubt It has been variously ascribed to deficient reabsorption of bicarbonate in the proximal tubule an inherent defect in ammonia production perhaps in tubular glutaminase activity an intrinsic error in the mechanism by which the tubular cell secretes hydrogen ion in exchange for sodium ions of the tubular urine and an inherent or drug induced deficiency of renal tubular carbonic anhydrase suggested by the many similarities between the naturally occurring disorder and that produced by protracted administration of acetazoleamide (alkaline urine hyperchloremic acidosis renal calculus formation) Appropriate loading and other tests however have not as yet fully substantiated any one of these several hypotheses

It is not clear whether variations in kind or in degree of defective tubular function are responsible for the diversity of clinical manifestations of renal tubular acidosis and whether the disorder encountered in young adults has the same genesis as that occurring in infants A familial incidence has been demonstrated in some cases implying an inherent tubular deficiency in at least these instances Tubular damage due to pyelonephritis has been incriminated but appears to be secondary Occurrence in infants may be related in part to delayed renal development since the urinary abnormalities may ultimately disappear

Symptoms and Signs The paradoxical excretion of an alkaline or only slightly acid urine in the face of a metabolic acidosis should direct attention to this syndrome There is apt to be diminished ability to concentrate the urine which may be excreted in such copious quantities as to cause marked dehydration notably in affected infants despite polydipsia The serum bicarbonate is reduced the serum chloride increased the serum phosphate and potassium levels are both low the serum alkaline phosphatase is increased when skeletal lesions are present

Three complications are particularly prone to occur in the adult type of the disease *nephrocalcinosis* or *renal calculus*

formation osteomalacia and profound *muscle weakness* Deposition of calcium within the kidney substance or as calculus with recurrent ureteral colic is favored by the alkalinity of the urine and possibly by reduced urinary citrate there is little to support the hypothesis of secondary hyper parathyroidism Pyelonephritis often super venes sometimes with progressive glomeru lar insufficiency The hypophosphatemia results from loss of phosphate in the urine and presumably is responsible for the ap pearance in the adult of osteomalacia with the characteristic manifestations of Milk man s syndrome and in children of rickets refractory to vitamin D There may be disturbances in skeletal growth or in the adult in gait Spontaneous fractures may occur Muscle stiffness or weakness with episodic periods of paralysis may be a presenting symptom as a consequence of potassium depletion due also to excessive loss in the urine The undue urinary excre tion of potassium presumably is a reflec tion of the defective hydrogen ion secre tion in acidification of the urine It is pos sible that renal tubular damage associated with potassium depletion may be superim posed upon the initial defect in some cases

As already mentioned *administration of carbonic anhydrase inhibitors* such as acetazoleamide may simulate the meta bolic disturbances characteristic of renal tubular acidosis Hyperchloremic acidosis with somewhat similar symptomatology occurs also after *ureterosigmoidostomy*

Treatment The response to appropriate therapy is gratifying Replacement of lost base by daily oral administration of an alkalinizing mixture of citrates effectively relieves the acidosis and restores electrolyte balance in most cases The manifestations of osteomalacia or rickets respond gratify ingly to vitamin D in doses of 50 000 units a day and calcium salts by mouth to avoid further renal damage however these should not be pushed to hypercalcemia and should be discontinued upon healing of the skeletal lesions Hypokalemic episodes re quire administration of potassium salts The use of sulfonamides which inhibit carbonic anhydrase should be avoided since exacerbation of symptoms may occur

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ALKAPTONURIA AND OCHRONOSIS*

Definition Alkaptonuria is a rare disorder of the metabolism of the amino acids tyro sine and phenylalanine characterized by the excretion of homogentisic acid in the urine

Pathogenesis It occurs most commonly in males and is transmitted according to re cent evidence as a dominant trait with incomplete penetrance not as a recessive as previously believed The metabolic block is complete and the amount of homogen tisic acid excreted is proportional to the amount of protein catabolized Homogen tisic acid is formed in the normal course of catabolism of tyrosine and phenylala nine but normally is wholly degraded by homogentisic acid oxidase and does not appear in the urine Recent studies by LaDu *et al* on liver tissue from an alkapto nuric patient have shown that homogen tisic acid oxidase is completely lacking in this disorder There appear to be no other defects in the metabolism of tyrosine and phenylalanine

Diagnosis The diagnosis is often sug gested early in life by diapers or linen stained black or brown by urine and by a family history of alkaptonuria

Urine The color of the urine is normal when acid and freshly excreted when alka line it may be dark When alkali is added it turns black It reduces Benedict s solu tion imparting a brown or black color to the supernatant fluid This appearance should suggest the presence of an abnormal reducing substance other than glucose Further identification can be made by more specific chemical tests and if the diagnosis still remains in doubt isolation of homo gentisic acid from the urine will establish the diagnosis with certainty

Ochronosis Ochronosis is a clinical state characterized by the deposition of bluish black pigment in the cartilages tendons and other types of connective tissue The term ochronosis was derived from the ochre like color of the pigment on histolog ical examination In time probably all alkaptonuric persons develop some degree of pigmentation but the intensity and

* The author wishes to express his deep apprecia tion to Dr Morton Galdston for his valuable as sistance in the revision of this article

distribution as seen clinically varies considerably In its fully developed form as seen in older alkaptonurics it is manifested by a patch of light brown or slate gray piment in the sclerae on either side of the corneal limbus by a bluish discoloration of the external ears nasal cartilage and superficial tendons of the hands and brown pigmentation in the skin cerumen sweat and the nails The pigmented ears are opaque to the transmission of light

The term *ochronosis* also applies to similar pigmentation associated with clinical conditions other than alkaptonuria It was formerly seen after long continued application of phenol dressings to leg ulcers and it may occur in association with melanuria The pigmentation observed after the use of phenol gradually recedes after the causative agent is discontinued In contrast the pigmentation associated with alkaptonuria by virtue of the permanence of the metabolic disturbance is persistent and progressive

In spite of the similarity in distribution and appearance of the ochronotic pigments their origin is distinct Alkaptonuric pigment is a derivative of homogentisic acid whereas melanotic pigment is derived from 3 4 dihydroxyphenylalanine (dopa) The enzyme tyrosinase catalyzes the oxidation of dopa to melanin but there is no reason to believe it is also involved in the polymerization of homogentisic acid to the ochronotic pigment The pathway by which phenol is converted to ochronotic pigment is unknown

Arthritis Pigment deposition in joint cartilages is accompanied by degenerative changes and arthritis The severity of the arthritis is not necessarily proportional to the degree of joint pigmentation but arthritis may be the chief complaint of middle aged alkaptonurics and it is a prominent feature of the condition The joints usually affected are the hip knee shoulder and the spine The rate of progression of the arthritis and the intensity of symptoms vary widely among different patients

Roentgenographic Findings Roentgenographic examination of the spine may show the presence of intense calcification of the intervertebral disks which is characteristic of the disease In addition degenerative osteoarthritic changes are generally apparent in the involved joints Calcific deposits are commonly seen in muscle tendons about the large joints Stones may be demonstrated in the urinary bladder prostate gland and the urethra

Prognosis The disease does not apparently decrease life expectancy Except for the passage of black urine and the appearance of pigmentation in the second and third decades as described under Ochronosis patients are relatively free of symptoms until the onset of arthritis in middle age

Treatment No specific treatment is available for alkaptonuria or for ochronosis associated with it Scorbutic guinea pigs fed phenylalanine or tyrosine excrete homogentisic acid in the urine and this defect is corrected by vitamin C In contrast clinical alkaptonuria is not due to a vitamin C deficiency and this vitamin has no effect on the metabolic defect The only effect of vitamin C in clinical alkaptonuria is that it delays to some degree the darkening of the urine because of its strong reducing properties A restriction of dietary protein has been advocated since this decreases the amount of homogentisic acid excreted per day and might theoretically decrease the rate of development of ochronosis The arthritis resembles osteoarthritis and should be treated similarly It does not respond favorably to agents found effective in rheumatoid arthritis such as ACTH cortisone and phenylbutazone

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PHENYLPYRUVIC OLIGOPHRENIA

(Phenylpyruvic Amentia Phenylketonuria)

Definition and Genetics Phenylpyruvic oligophrenia first described by Folling in 1934 is a hereditary disease characterized by mental deficiency and by a metabolic aberration failure in the hydroxylation of phenylalanine to tyrosine manifested by urinary excretion of phenylpyruvic acid Genetic studies have proved that the condition is transmitted as a simple mendelian recessive trait Jervis studied 125 families and found 52 in which more than one

sibling was affected Penrose studied the families of 203 initial cases and found that 129 of 638 siblings were affected in 30 of the 203 families the parents were first cousins

Incidence The reported incidence varies in different countries and probably depends on the awareness of investigators In the United States and Great Britain where extensive genetic clinical and metabolic studies have been conducted the over all incidence is about 1 25 000 and 1 50 000 respectively in institutions for the feeble minded 0 3 to 0 8 per cent of inmates of all ages In Norway Folling and his associates discovered 34 cases or 1 4 per cent of about 2400 mental defectives tested Swiss investigators found only 3 cases in tests on about 2500 mental defectives One case has been reported in a Jewish child The disease is extremely rare in non white persons

Clinical Findings The most striking clinical finding is mental deficiency generally of severe degree Psychometric tests of institutionalized phenylketonurics place about 60 to 65 per cent in the idiot range (I Q below 20) and 30 to 35 per cent in the imbecile range (I Q 20 to 50) Several patients have been reported with I Q s over 80 Probably more with normal or nearly normal intelligence will be discovered outside of institutions

Patients usually come to the physician s attention by one of three routes (1) search among institutionalized mental defectives (2) detection of the urinary abnormality in siblings of known cases or by routine ferric chloride test in "well baby examinations or (3) symptoms such as slow development lethargy or convulsions The infants may appear normal at birth but in a few weeks show lack of interest in surroundings and delay in motor development They usually are good natured but often exhibit temper tantrums

The physical appearance of these patients is usually characteristic and distinctive from that of patients with other specific and nonspecific forms of mental deficiency More than 85 per cent of phenylketonurics have blond hair and fair complexion often lighter in coloring than their parents and normal siblings The younger children usually have attractive facies Stature and head size may be average or small

The frequency and variety of skin manifestations are probably related to diminished skin pigment They range from dermatographia photosensitivity and increased sweating to eczema which may be patchy and transient or extensive and intractable

The nervous system is frequently but variably involved Clumsiness and hyperactive reflexes are almost universally present the patients learn to walk late (two and one half to eight years) and many have a stiff jerky short stepped gait often associated with kyphotic posture or a semirigid forward bending at the hips Stereotyped repetitive motions including head nodding and so-called "digital mannerisms" sometimes described as athetoid are common fine tremors are less common When epileptiform seizures are present their frequency tends to diminish after the age of nine or ten years Phenylketonurics of higher intelligence may have normal posture and gait and show no neurological stigmata The abnormal neurological findings are believed by some to comprise an extrapyramidal syndrome but most investigators consider them nonspecific The electroencephalogram is usually abnormal (79 per cent in Paine s series) Spike and wave complexes of the petit mal variant type are frequently found even in patients without epilepsy

Metabolic Aberration Diagnosis is confirmed by simple qualitative chemical test of freshly voided urine To 5 ml of urine acidified with dilute sulfuric acid add a few drops of fresh 5 per cent ferric chloride solution or drop the ferric chloride reagent directly on a freshly wet diaper if phenylpyruvic acid is present a deep bluish green color appears immediately Most phenylketonurics excrete from 0 5 to 2 0 gm of phenylpyruvic acid daily However the test may not become positive until four or five weeks of age Rarely the urine of normal adults receiving high phenylalanine doses may give a positive test

Blood concentrations of phenylalanine and phenylpyruvic acid are high The urine contains a number of derivatives of these compounds phenyllactic acid phenylacetic acid phenylacetyl glutamine and o hydroxyphenylacetic acid and also tryptophane derivatives indoleacetic and indolelactic acids in amounts far beyond normal

The essential metabolic defect is an inability to convert phenylalanine to tyrosine by hydroxylation in the para position Phenylalanine can be transaminated to its keto analogue phenylpyruvate This keto acid accumulates in the blood and is partially excreted unchanged in the urine the remainder being converted enzymatically to yield phenyllactate by reduction and phenyl

acetate by oxidative decarboxylation The phenylacetate is conjugated with glutamine to form phenylacetylglutamine

Folling was the first to postulate a primary enzymic defect in the conversion of phenylalanine to tyrosine Jervis and Udenfriend and associates have demonstrated the presence of a phenylalanine hydroxylase in the liver of normal human beings and its absence in the liver of phenylketonuric subjects Mitoma and his associates and Wallace and co workers have shown that phenylalanine hydroxylase is present in rat liver in two fractions I a labile fraction found only in liver and II a stable fraction found in many tissues including liver and brain Their evidence *suggests that the enzyme lacking in phenyl* pyruvic oligophrenia is similar to rat liver fraction I

The relationship of the mental defect to the metabolic disorder is the subject of much active research The two defects conceivably are merely concurrent inherited in the same gene The reports of Bickel (1954) Armstrong (1955 1957) and others however indicate that in some patients the mental status seems to be favorably altered by a diet low in phenylalanine The view that the mental retardation is secondary to the chemical aberration is a more fruitful working hypothesis more consistent with available evidence and offers the only rational basis for therapy

The exact manner in which central nervous system development and function are damaged whether it is by a toxic effect of phenylalanine or of one or more of its metabolic products or by some other mechanism is not known

The deficient ectodermal pigmentation may be the result of an inhibition of tyrosine *metabolism by the excessive phenyl* alanine tissue levels (possibly because L phenylalanine competes with tyrosine for the enzyme) Both high tyrosine dosages and a low phenylalanine intake with adequate tyrosine have been accompanied by increased hair pigmentation in some patients

Pathological Findings The pathological picture is variable The following central nervous system abnormalities have been described in isolated cases edema of the brain cord and optic nerves gliosis degeneration of myelin multiple nerve tumors and hypoplasia of the hypophysis Other cases have shown only a diminished size of the brain None of these findings is specific

Prognosis The prognosis for normal or even fair mental development is extremely guarded even in patients treated early in infancy and for others it is very poor Prognosis for life in a sheltered environ*ment is good though in the low grade pa*tients there is the same liability to succumb to intercurrent infection that is found in other idiots

Treatment A diet low in phenylalanine corrects most or all of the abnormal chem*ical findings in the blood and urine* In some patients beneficial clinical effects have been described most striking when the treatment is begun before the age of two years These are listed by Armstrong as follows increased attention span in*creased response to environment decreased* hyperactivity of tendon reflexes decreased spasticity and elimination of the dermatitis A diminution in the frequency of seizures and improvement in the electroencephalogram also occurred In some patients after several weeks of treatment there was regression in others stabilization and in a few remarkable progression Two children who began the corrective diet in the early months of life and were taken off at twenty three and twenty nine months respectively maintained I Q s of 85 after discontinuation of treatment for two years and for five months respectively He postulates a critical age period from four months to two years during which damage to the central nervous system in phenylketonuria occurs

The low phenylalanine diet which is commercially available is prepared from a protein hydrolysate from which phenylalanine is removed and to which other amino acids minerals and choline are added The patient also receives supplemental vitamins *carbohydrate and fat Initially* 5 gm of the basic mixture per kg of body weight is offered Blood phenylalanine level is determined weekly until the normal value of 1 0 to 2 0 mg per 100 ml is reached Low protein foods are then added to supply the minimum amount of this essential amino acid needed for growth (15 to 90 mg per kg of body weight)

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HEPATOLENTICULAR DEGENERATION
(*Wilson s Disease*)

The disorder known as Wilson s disease is a familial coarsely nodular cirrhosis of the liver which in some patients is associated with progressive damage to the nervous system resulting in the appearance of tremor and rigidity There are two chief types of the disease One is a more rapidly progressive disorder appearing in late childhood or early adolescence with rigid posture and pseudobulbar symptoms in addition to tremor the "progressive lenticular degeneration of Wilson The other is a lowly progressive disorder characterized chiefly by tremor and titubation appearing in the third or fourth decade and running a course of many years (pseudosclerosis) Intermediate mixed types are more common than these extremes

Pathology Some degree of coarsely nodular cirrhosis of the liver is found in all cases with variable extent of recent degeneration of some lobules of the type seen in acute yellow atrophy Regenerative activity is intense In a few cases portal obstruction and its effects are obvious but in most this is minimal

The nervous system may appear normal to the naked eye except for some shrinkage of the basal ganglia and brownish pigmentation of the putamen (the outer segment of the lenticular nucleus) Throughout the central nervous system but most evident in the cerebral cortex basal ganglia thalamus and dentate nuclei there is a great increase in number of the large astrocyte nuclei These astrocytes are sometimes present in lobulated or even giant cell forms with light brown pigment in the cytoplasm In the more rapidly progressive forms of the disease edematous areas in the glia appear in the frontal cortex lenticular and dentate nuclei When intense this process leads to the appearance of cavitation in these situations as originally described by Wilson

The pigmentation of the cornea is present in fine granules in Descemet s membrane and has been shown chemically and spectroscopically to contain chiefly copper with traces of zinc and other metals The pigment in the cerebral glia the liver and occasionally the skin appears to be identical The copper content of the liver and of the brain especially the basal ganglia is greatly increased There is no evident renal lesion and in distinction from the Fanconi syndrome the first collecting tubule is reported to be of normal length

Symptoms and Signs In some families the cirrhosis is a prominent feature and episodes of ascites or hematemesis are frequent More commonly symptoms of liver damage are entirely absent though cirrhosis is invariably present in some degree Jaundice is not a symptom and tests of liver function are usually not helpful unless there has been clinical evidence of a recent hepatic embarrassment Cephalin and thymol flocculation have been the most frequently positive liver function tests Liver biopsy with histochemical staining of copper by rubeanic acid is the most specific test

The disease is characterized by a consistently high output of amino acids and copper in the urine so that up to 10 gm of amino acids and 1000 micrograms of copper may be excreted in twenty four hours The biliary excretion of copper is normal There is an overabsorption of copper from the alimentary tract and an increased deposition of copper in all organs Cu^{64} studies indicate that the urinary copper is derived from the copper released from tissues rather than that directly absorbed In the plasma there is a reduction of the blue copper protein caeruloplasmin and the related oxidase activity The total copper level is little altered for though this indirect fraction is low the direct copper fraction is abnormally high Caeruloplasmin could have only a minor function in producing an overabsorption of copper The overabsorption may be a result of an increased affinity for copper that the tissue proteins intrinsically possess biochemically demonstrable in liver and cornea in this disease

The patient may succumb to the effects of hepatic cirrhosis without developing neurological symptoms other than terminal coma More commonly tremor and dystonia with pseudobulbar phenomena in the form of dysarthria and fixed smiling expression appear In the more rapidly progressive forms of the disease dystonic attitudes such

as overpronated postures of the arms choreic movements inversion of the feet open mouthed fixed smile with difficulty in mental concentration first appear between the ages of fourteen and eighteen the earliest age reported being four years In a few months the limbs may become greatly distorted by dystonic rigidity and slow rhythmical tremors appear leading to a termination in one to three years If the onset occurs after the age of eighteen to twenty the course is slower and the characteristic tremor is prominent When the neurological disorder appears after the age of twenty five tremor and dysarthria may be the only signs associated with slow mental deterioration The tremor is a flapping of the hands at the wrist as in waving good bye and is present when the hands are outstretched It is then accompanied by alternating adduction abduction at the shoulder Titubation of the head and dysarthria are common indicating that the essential tremor is cerebellar in type In more progressive types of the disease a plastic rigidity of the limbs and set expression of the face appear and in time the pill rolling tremor of the fingers of parkinsonian type is added The lower limbs then also become affected

Pigmentation of the outer margin of the cornea in the form of a smoky brownish ring (the Kayser Fleischer ring) seen best by oblique lighting is absolutely characteristic of this disease It is constant in the more chronic forms but may be absent in the more rapidly progressive forms of the disease

Treatment Treatment by diets designed to favor liver function has not had any lasting effect on the neurological symptoms Improvement sometimes striking in degree has followed the periodic mobilization of copper deposits by BAL (2 3 dimercapto propanol) 1 0 to 1 5 ml of 10 per cent solution in peanut oil intramuscularly once weekly for an indefinite period Such improvement has been maintained for eight years in one patient and between five and seven years in five others These were all cases of the pseudosclerotic type who ultimately succumb from progressive portal obstruction after many years with or without chelation The dystonic form of the disease also usually shows improvement with chelation but within a period of one to three years develops a periodic Jacksonian convulsive disorder that does not respond to chelation Each such attack brings further dystonia without fresh hepatic damage and ultimately death in coma The cause of this type of relapse which can also occur without specific treatment and without fresh liver damage is unknown Other chelating agents such as versene and penicillamine have received limited trials Alternation of high and low protein diet also increases copper excretion Potassium sulfide 20 mg in enteric coated capsules is given in one capsule with each meal to render copper in the diet insoluble No satisfactory way of eliminating copper from the diet has been found General anesthetics and barbiturates are very poorly tolerated but cyclopropane ether has been successfully used in five reported cases

D DENNY BROWN

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FAMILIAL PERIODIC PARALYSIS

This syndrome is characterized by periodic attacks of flaccid paralysis usually involving the muscles of all four extremities and the trunk but occasionally affecting only the arms or legs The condition is hereditary has its onset during the first or second decade of life and persists for a number of years The attacks usually develop during the night and if untreated last for a few hours to a few days Attacks may recur daily or may be separated by intervals of a year or more The tendon reflexes are abolished the muscles can be

completely refractory to all types of stimu lation and during particularly severe at tacks cardiac and respiratory involvement can occur Sensation and mental faculties are not impaired During periods between attacks the findings are normal

Pathological Physiology The attacks of paralysis are typically associated with hypo-kalemia and in susceptible subjects may be precipitated by measures that decrease the concentration of potassium in the serum *e g* the ingestion of a large amount of carbohydrate the concomitant admin istration of glucose and insulin or the administration of a "salt retaining" steroid *or of epinephrine However there is no* consistent correlation between the onset and intensity of attacks and the degree of depression of serum potassium levels The ratio between potassium in intracellular and extracellular water is about 30 1 con sequently quite large variations in intracel *lular potassium may occur without detect* able change in serum levels There is evidence suggesting that during an attack potassium is shifted to an intracellular site and that the atack is not characterized by urinary loss of potassium or sodium On the other hand Conn has shown that at *tacks are preceded by the retention of* sodium with concomitant fall in serum potassium and a sharp rise in urinary aldo-sterone Recovery is associated with changes in the opposite direction Measures known to induce attacks in the presence of a normal or high intake of sodium may *fail to do so when sodium intake is sharply* curtailed Conn believes the primary dis turbance may be an increase in intracellu lar sodium and that sudden alterations in potassium metabolism may be contributory to the induction or alleviation of paralysis

Differential Diagnosis Familial periodic *paralysis must be distinguished from other* disorders in which muscle weakness is associated with detectable disturbances in potassium metabolism These include pri mary aldosteronism Cushing s syndrome potassium losing nephropathies (*e g* renal tubular acidosis) excessive administration of diuretics including chlorothiazide and mercurials diarrheal disorders including the excessive use of cathartics with associ ated loss of potassium and steroid therapy In all of these disturbances as well as in familial periodic paralysis the electrocardi ogram may show the changes characteristic of hypokalemia

Muscular weakness and paralysis may be associated with hyperkalemia occurring under different conditions *e g* in ad vanced renal disease in sodium depletion and in a hereditary syndrome designated *adynamia episodica hereditaria* This latter disorder resembles familial periodic paraly sis in many respects and could be confused with it However all these types of hyper kalemia may be associated with paresthe sias and show increased levels of serum potassium as well as electrocardiographic changes typical of hyperkalemia Admin istration of potassium does not improve symptoms and indeed may have pro-nounced paralytic effect It should be em phasized that in all of these syndromes definitive diagnosis may require more than *a single observation of the serum potassium* or the electrocardiogram

Treatment, Prevention and Prognosis At tacks may be terminated in a few hours by the oral administration of 5 to 15 gm of potassium chloride For prevention of frequently recurring attacks restriction of *dietary sodium is recommended the daily* administration of 10 to 30 gm of potas sium chloride is often of great value

The prognosis for life is usually excel lent and attacks often decrease in fre quency and intensity over the years Very occasionally patients succumb from respira *tory failure*

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PORPHYRIA

Definition and Classification Porphyria may be defined as a constitutional fault or inborn error" in porphyrin metabolism It is probably best to limit the term to cases in which uroporphyrin and/or porphobilino gen are excreted in great excess since this characterizes the constitutional abnormal ity Thus used the term porphyria em

as overpronated postures of the arms choreic movements inversion of the feet open mouthed fixed smile with difficulty in mental concentration first appear between the ages of fourteen and eighteen the earliest age reported being four years In a few months the limbs may become greatly distorted by dystonic rigidity and slow rhythmical tremors appear leading to a termination in one to three years If the onset occurs after the age of eighteen to twenty the course is slower and the characteristic tremor is prominent When the neurological disorder appears after the age of twenty five tremor and dysarthria may be the only signs associated with slow mental deterioration The tremor is a flapping of the hands at the wrist as in waving good bye and is present when the hands are outstretched It is then accompanied by alternating adduction abduction at the shoulder Titubation of the head and dysarthria are common indicating that the essential tremor is cerebellar in type In more progressive types of the disease a plastic rigidity of the limbs and set expression of the face appear and in time the pill rolling tremor of the fingers of parkinsonian type is added The lower limbs then also become affected

Pigmentation of the outer margin of the cornea in the form of a smoky brownish ring (the Kayser Fleischer ring) seen best by oblique lighting is absolutely characteristic of this disease It is constant in the more chronic forms but may be absent in the more rapidly progressive forms of the disease

Treatment Treatment by diets designed to favor liver function has not had any *lasting effect on the neurological symptoms* Improvement sometimes striking in degree has followed the periodic mobilization *of copper* deposits by BAL (2 3 dimercapto propanol) 1 0 to 1 5 ml of 10 per cent solution in peanut oil intramuscularly once weekly for an indefinite period Such improvement has been maintained for eight years in one patient and between five and seven years in five others These were all cases of the pseudosclerotic type who ultimately succumb from progressive portal obstruction after many years with or without chelation The dystonic form of the disease also usually shows improvement with chelation but within a period of one to three years develops *a periodic jacksonian* convulsive disorder that does not respond to chelation Each such attack brings further dystonia *without* fresh hepatic damage and ultimately death in coma The cause of this type of relapse which can also occur without specific treatment and without fresh liver damage is unknown Other chelating agents such as versene and penicillamine have received limited trials Alternation of high and low protein diet also increases copper excretion Potassium sulfide 20 mg in enteric coated capsules is given in one capsule with each meal to render copper in the diet insoluble No satisfactory way of eliminating copper from the diet has been found General anesthetics and barbiturates are very poorly tolerated but cyclopropane-ether has been successfully used in five reported cases

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FAMILIAL PERIODIC PARALYSIS

This syndrome is characterized by periodic attacks of flaccid paralysis usually involving the muscles of all four extremities and the trunk but occasionally affecting only the arms or legs The condition is hereditary has its onset during *the first* or second decade of life and persists for a number of years The attacks usually develop *during the night and* if untreated last for a few hours to a few days Attacks may recur daily or may be separated by intervals of a year or more The tendon reflexes are abolished the muscles can be

the urine in the erythropoietic and the pure cutanea tarda types and conversely is prominent in the intermittent acute type in which skin lesions are not a feature In the photosensitive types uroporphyrin is readily demonstrable in the circulating blood whereas this is exceptional in the intermittent acute types

Although the urine in acute porphyria contains large amounts of porphobilinogen and its immediate precursor delta amino levulinic acid there is no evidence that either of these compounds is directly responsible for the abdominal or nervous manifestations of the disease The mechanism of their production remains unexplained

In the erythropoietic (congenital) form the teeth may be red or reddish brown (erythrodontia) According to Garrod this is an evidence that the excessive formation of uroporphyrin began during fetal life At necropsy the bones are red in varying degree owing to deposition of uroporphyrin The bone marrow is usually hyperplastic and normoblastic often in association with splenomegaly and hemolytic anemia

In this form of the disease many of the normoblasts of the bone marrow contain large amounts of porphyrin This has been shown to be a mixture of uro copro and protoporphyrin The nuclei are especially rich in porphyrin content as shown by fluorescence microscopy Circulating erythrocytes also contain marked excesses of uro and coproporphyrin and the spleen is rich in these substances probably because of the excessive destruction of erythrocytes and storage of the porphyrin which they contained Lesser amounts are found in the liver In certain instances splenectomy is followed by a marked and sustained reduction of porphyrin formation in the bone marrow This is believed due to a reduced erythropoiesis dependent upon a reduced rate of blood destruction as a consequence of the splenectomy

Evidence of liver injury or liver disease is frequently encountered in the hepatic types Clinical evidences of hepatic disturbances are discussed in the following section Liver biopsy or examination of the liver at necropsy may reveal varying degrees of fatty liver cirrhosis or liver cell injury Fluorescence microscopy in the cutanea tarda type reveals large amounts of preformed uroporphyrin In the intermittent acute type there is relatively little fluorescence but porphobilinogen is readily demonstrated In the combined or mixed type varying transitions are observed and there is evidence that the ratio of non fluorescing precursor to porphyrin varies from time to time In the hepatic forms of porphyria the bone marrow porphyrin content is normal and porphobilinogen is not demonstrable

Inconstant and nonspecific changes have been observed in the nervous system from time to time in fatal cases of the intermittent acute type Microscopic changes indicative of nerve cell injury have been described in both the central nervous system and the sympathetic ganglia Recent observations point strongly toward an important role of the sympathetic nervous system in relation to certain of the manifestations of the intermittent acute type notably abdominal pain and hypertension Tetraethylammonium chloride often relieves the pain and lowers the blood pressure In one instance in which there had been abdominal pain almost daily for a long period complete relief has been afforded by splanchnicectomy for at least two years after the procedure was carried out

Symptoms and Signs In the photosensitive types the earliest symptom is most often the appearance of small bullae or vesicles on the face or hands after exposure to sunlight with production of the syndrome of hydroa aestivale seu vacciniforme" As will be emphasized later porphyria is by no means the only cause of this syndrome

In some instances of the hepatic cutanea tarda type the skin lesions may be urticarial or eczematoid These patients often exhibit in addition an increased brownish pigmentation of the skin It should be noted that brownish pigmentation of an addisonian type may also occur in cases of intermittent acute porphyria in the absence of any photosensitivity Brunsting and others have emphasized that in the cutanea tarda type vesicles are often caused by heat and trauma as well as by light As Brunsting has pointed out the face in this type at times presents a peculiar violaceous hue

Varying degrees of hirsutism are often observed especially in the erythropoietic form of the disease at times in the hepatic cutanea tarda rarely in the intermittent acute form The basis of this is unknown

In contrast to the paucity of visceral manifestations in the pure photosensitive type the variations in symptomatology and physical findings in the intermittent acute and combined hepatic types have undoubtedly been responsible in many instances

braces two fundamentally distinct groups (1) erythropoietic (2) hepatic The former is synonymous with what Gunther described as porphyria congenita The latter includes (a) the intermittent acute form (b) the cutanea tarda type (Gunther's "chronic" porphyria) (c) the combined or "mixed type (d) latent porphyria There is reason to believe that there are at least two genetic variants of acute porphyria According to Waldenstrom the form observed in Sweden exhibits no relationship to the cutanea tarda type while in the families studied by Dean in South Africa all of the types of hepatic porphyria are represented Certain differences in the porphobilinogen and porphyrin excretion during remission and in latent cases have also been noted and will be mentioned again

Incidence The erythropoietic (congenital) form of the disease is distinctly rare Many of the cases described in the literature as congenital porphyria are undoubtedly of the hepatic cutanea tarda type differing fundamentally from the erythropoietic disease The hepatic intermittent acute type is the most common form of porphyria It has often been overlooked because of its close mimicry of various other pathological states Of 203 well documented cases of all types collected by the author only 6 were erythropoietic the remainder were hepatic of which 119 were of the intermittent acute type 34 were of the cutanea tarda type 11 were combined or mixed and 33 were latent

Although it has been believed that striking differences in sex incidence exist between the congenital and acute types of porphyria recent studies based on the above mentioned fundamental classification fail to reveal any significant sex difference in the erythropoietic type but the hepatic intermittent acute form is somewhat more common in females The ratio in 119 cases was about 1 5 1 0 The cutanea tarda form is distinctly more frequent in males a ratio of 26 to 8 being noted in 34 cases The age at onset of manifestations is much earlier in the erythropoietic disease usually in infancy or early childhood the condition in some instances being evident at birth In the hepatic forms symptoms are rarely noted before puberty the age at onset more often being in the third or later decades

Etiology Erythropoietic porphyria is an "inborn error due to a non sex linked recessive gene Hepatic porphyria in its various forms is also familial a non sex linked dominant genetic trait

Gunther and others used the term *toxic* acute porphyria to imply that some cases were acquired *on the basis of chemical* poisoning There can be no doubt that acute attacks are often *precipitated by chemicals* in the hepatic intermittent acute form of the disease Sulfonal Trional barbiturates and less frequently a variety of other chemicals even including alcohol have been implicated Waldenstrom and others have clearly demonstrated that barbiturates may precipitate attacks in individuals having latent porphyria previously free of symptoms Such latent cases were identified because other members of the patient's families had manifest disease The exact mechanism by which chemicals precipitate attacks is unknown This variety of porphyria is to be distinguished sharply from the ordinary symptomatic or *secondary coproporphyrinuria* Coproporphyrin is normally present in urine and feces and is increased in a variety of pathological states including lead and other heavy metal poisoning chemical toxicity (especially benzene ring compounds) hepatic disease certain afflictions of the nervous system and in some of the anemias The secondary porphyrinurias constitute a separate topic quite distinct from that of porphyria and will be considered here only from the standpoint of differential diagnosis

On occasion considerable excesses of porphobilinogen and/or uroporphyrin are found in the urine in cases of severe diseases such as carcinomatosis Hodgkin's disease systemic infections nervous system disease or advanced liver disease in which the ordinary clinical manifestations of porphyria are lacking The reason for the increased excretion of these substances in such cases is not clear The possibility has been considered that they represent latent porphyria in association with an other disease such as mentioned

Morbid Anatomy and Pathological Physiology In the photosensitive types the principal lesions are those due to light sensitivity of the exposed areas of skin viz the face ears and hands

It has thus far been impossible to reproduce skin lesions by artificial light of the wave length believed optimal on the basis of the uroporphyrin absorption spectrum Nevertheless uroporphyrin I is a strongly photosensitizing substance and it is reasonable to believe that it is responsible for the skin lesions perhaps on the basis of repeated or chronic sunlight exposure Porphobilinogen is entirely lacking from

tion to being a porphyrin precursor gives rise to porphobilin a dark brown non porphyrin pigment of unknown chemical structure Probably because of its content of this pigment the urine of the intermittent acute type of porphyria is darker with more brown and less red color than that of the pure photosensitive types Porphyria urine usually contains an excessive amount of coproporphyrin The porphyrin and pigment content of the urine is much more complex in the intermittent acute than in the photosensitive type of the disease

Differential Diagnosis The possibility of porphyria should be borne in mind in the presence of any obscure nervous disturbance especially unexplained peripheral neuritis flaccid paralyses of extremities bulbar palsy and hysteria It should also be searched for in any instance of abdominal pain which is otherwise unexplained Among other conditions the disease has been confused in the past with gallstone colic renal colic appendicitis bowel obstruction and lead poisoning In the last the urine regularly contains a marked increase of coproporphyrin but rarely any marked excess of porphobilinogen or uroporphyrin nor is the amount of coproporphyrin sufficient to color the urine red In gallstone colic the urine Ehrlich reaction may be positive because of excessive urobilinogen Confusion of porphyria with renal colic has usually been due to the belief based on superficial examination that the red urine was due to blood and the pain due to ureteral calculus Careful examination of the urine will obviate this mistake The lack of rebound tenderness and muscle spasm together with the urinary findings serves to distinguish porphyria from appendicitis The leukocyte count is usually normal but in exceptional cases may be considerably elevated The roentgenographic findings aid in excluding bowel obstructions the characteristic layering of the small bowel not being observed Areas of marked alternating spasm and distention of the large bowel are rather common especially of the transverse colon and splenic flexure In rare instances volvulus and gangrene of the cecum or strangulation of small bowel has been a sequel of the attack

Hypertension is noted in some cases and it is of interest that lumen attenuation of retinal arteries of spastic type may be seen in such instances During the acute attack the hypertension may be associated with oliguria and these manifestations coupled with the dark urine may give rise to a superficial resemblance to acute glomerulonephritis If the attack subsides and the disease becomes quiescent or latent the blood pressure returns to normal and retinal vascular abnormalities may disappear entirely Electrocardiographic changes are observed in some cases

At times the persistent tachycardia and muscle weakness may be suggestive of hyperthyroidism in other cases weakness and pigmentation give rise to consideration of Addison s disease The pigmentation is present in but a minority of cases It is usually rather patchy in character in some cases associated with intervening vitiligo The nature of the pigment has not been determined In one case seen by the writer the patient at an earlier age had had an appendectomy which failed to relieve the attacks of abdominal pain for which it was done several years later she underwent a thyroidectomy because of tachycardia weakness and nervousness later still in another hospital she received salt and adrenal extract treatment for supposed Addison s disease on the basis of weakness and mild pigmentation of the skin Subsequently this patient had severe abdominal pain and paralyses of all four extremities from which however she recovered completely Fourteen years later she had had no recurrence of symptoms and at this time the urine and fecal porphyrins were entirely normal

Occasional cases are observed in which chronic constipation and long standing abdominal pain are prominent and in which the urine contains a several fold increase of coproporphyrin but neither porphobilinogen nor increase of uroporphyrin A satisfactory classification of these cases is impossible at the present time but it does not appear that they should be included in the category of true porphyria As a matter of fact they will not be recognized as involving any disturbance of porphyrin metabolism unless a quantitative study of coproporphyrin excretion is made

Many cases of "hydroa aestivale seu vacciniforme" bear no relation to porphyria although the skin lesions may be indistinguishable In some of these it is evident that ordinary window glass prevents the photosensitivity since it absorbs the exciting light (below 3000 Å) In the photosensitive types of porphyria the wave length of the light most important in inducing skin lesions is probably in the neighborhood of 4000 Å with the result that window glass is not protective

Prognosis In the erythropoietic photo

for confusion in diagnosis For the most part the symptoms are either nervous or abdominal in character not infrequently both are present in the same case In the combined type photosensitive skin lesions are added in varying degrees They may precede coexist with or follow the nervous and/or abdominal manifestations

The *nervous manifestations* may be referable to any part of the nervous system central peripheral or autonomic The more acute attacks of the disease may be preceded for many years by undue nervousness neurasthenia or mild hysteria More severe psychic abnormalities ranging from marked hysterical behavior or outspoken psychoses of manic depressive or Korsakow type to delirium or coma have been described Epileptiform convulsions or even typical grand mal seizures may occur Various cranial nerve involvements have been reported with resulting manifestations which include optic atrophy eye muscle palsies dysphagia and persistent tachycardia Hoarseness due to vocal cord weakness or outspoken paralyses of the skeletal muscles are often noted These are usually patchy at least at the outset although in many instances all four extremities become involved to the extent of a rather complete flaccid quadriplegia with marked wrist and foot drop *The disease has been confused* with Landry s ascending paralysis but as Waldenstrom has emphasized the paralysis of porphyria is usually not of the ascending type or symmetrical in development In some cases but one or two extremities are involved and there may be nothing more than distinct weakness The deep reflexes are hypoactive or entirely absent At times there is hyperactivity of the Achilles reflexes or even outspoken clonus with absence of knee jerks In developing paralyses muscle atrophy and contractures commonly ensue although the extent to which recovery may occur between attacks is often more surprising The appearance of weakness of the extremities is often preceded and accompanied by persistent severe pain similar to that observed in some cases of diabetic neuritis The pain is stubborn and difficult to control and is often worse during the night The *abdominal* pain is also severe and usually colicky It may be generalized or localized to any part of the abdomen or loins Abdominal distention may be present but the lack of muscle spasm and rebound tenderness is usually in contrast to the severity of the pain Marked constipation is the rule although exceptional cases exhibit diarrhea

Diagnosis The examination of the urine for porphobilinogen and uroporphyrin is paramount Porphobilinogen is the name which Waldenstrom gave to the colorless precursor of the two principal pigments of porphyria urine It has recently been shown to be a monopyrrol while the porphyrins are tetrapyrrolic As already mentioned this chromogen does not occur in the urine of the erythropoietic or hepatic cutanea tarda type and is observed in cases of the combined type only in association with abdominal or nervous manifestations

The photosensitive types are characterized by the presence of large amounts of uroporphyrin with the result that the urine is red and at once attracts attention Spectroscopic examination readily permits identification of the uroporphyrin Interestingly enough the small amounts of uroporphyrin excreted in the intermittent acute cases are mainly zinc complex while in the erythropoietic type it is present chiefly at least as the free porphyrin The significance of the zinc complex is not clear It has been observed however in cases of "mixed type with photosensitivity but during complete remission of abdominal or nervous symptoms thus a causal relationship with the latter appears unlikely

The urines from cases of the intermittent *acute type need not be abnormally* colored even during the acute attack although in most cases the patient will have noticed a darkening of the urine at the outset Porphobilinogen is usually present in large amounts at this time If the fresh urine is normal in color the diagnosis may be overlooked unless the chromogen is sought for If the urine is allowed to stand in the light to bring about the characteristic darkening the uroporphyrin (metal complex) spectrum is then readily detected The porphobilinogen is demonstrable in fresh urine by means of the Ehrlich aldehyde test The resulting red compound is chloroform insoluble a *fact which serves to* distinguish it from urobilinogen aldehyde During relapse of acute porphyria the porphobilinogen aldehyde reaction is invariably strong and unmistakable If the reaction is a faint pink questionable or absent it is quite unlikely that symptoms are on the basis of porphyria In remission porphobilinogen may disappear from the urine quite completely as is characteristic of the South African cases or it may persist undiminished as is often true in the Swedish cases Wide variations are evident in this regard in cases observed in the United States Porphobilinogen in addi

some cases Patients with latent porphyria should be given a written statement concerning the diagnosis and danger of barbiturates and other chemicals to carry on their person at all times

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Gout and Gouty Arthritis

Gout is a disease of unknown origin characterized by (1) acute recurrent arthritis sometimes chronic arthritis later (2) slow accumulation of sodium biurate manifested by hyperuricemia and tophi and (3) secondary lesions affecting the kidneys "Acute gout" is a misnomer gout *per se* is always chronic

Gout is seen commonly if kept in mind It is not the disease but an awareness thereof which "disappears" from time to time

Predisposing Factors About 95 per cent of patients are males The reported incidence of active familial gout has been low (7 to 18 per cent) among American patients much higher (22 to 80 per cent) among British patients Heredity is more apparent among juveniles than adults with gout Gout occurs mostly in temperate zones It is common in England and France less common in North America Scandinavia Poland and Russia and almost unknown in the Orient and tropics Negroes are rarely affected Habitual or episodic excesses of food and drink probably do not predispose to gout *per se* but they may incite acute gouty arthritis They are provocative not predisposing factors Gout can occur in vegetarians and teetotalers Although the incidence of gout is higher among patients with blood dyscrasias such as myeloid metaplasia polycythemia and leukemia ("secondary gout") most patients so afflicted do not develop acute gouty arthritis even if hyperuricemia is present

Morbid Anatomy In gout urates tend to deposit in cartilage (ears joints rarely the nose) epiphysial bone other articular structures and kidneys rarely elsewhere Crystalline urates produce local necrosis and (unless tissue is avascular) an ensuing foreign body reaction with proliferation of fibous tissue the "gouty granuloma" Cartilaginous degeneration synovial proliferation destruction of subchondral bone ("destructive arthritis") proliferation of marginal bone ("hypertrophic arthritis") often synovial pannus and sometimes fibrous or bony ankylosis may slowly develop In the kidneys one finds gross and microscopic urate deposits in tubules medulla and interstitial tissues linear streaks in the pyramids and uratic gravel or calculi Secondary destructive and inflammatory reactions develop Thus the "gouty kidney" may appear as focal pyelonephritis nephrosclerosis or chronic glomerular nephritis (fibrosis hyalinization)

Nonspecific lesions such as atherosclerosis of the blood vessels of the heart and brain occur in gouty subjects but it is not clear whether the incidence is higher than in nongouty persons of similar age

Evolution of Symptoms Clinical Stages of Gout The chief features (arthritis hyperuricemia tophi late renal complications) are the outward signs of a fundamental disturbance of which little is known This disturbance ("gouty diathesis gout *per se*) is in operation long before it first manifests itself as *clinical gout* The successive phases of the development of the disorder may be designated the "carrier stage the stage of acute recurrent arthritis with complete remissions and the stage of *chronic gouty arthritis* *It should be* emphasized that the terms gout and gouty arthritis are not synonymous the latter is merely the dominant *symptom* of gout

The Carrier Stage While "hereditary hyperuricemia is genetically transmitted and the trait therefore is present in the newborn it is not detectable for a prolonged period In the male this latent stage usually lasts until puberty (when asymptomatic hyperuricemia ordinarily makes its appearance) in the female not until later

sensitive type the outlook for life is relatively good the disease having a long chronic course and death being due to intercurrent affections of one kind or another In some instances however severe anemia hemolytic in character is the most important governing factor in prognosis In the intermittent acute type the mortality is relatively high especially in cases with nervous system manifestations In the past a figure of 80 per cent within five years from the time of the first attack has generally been accepted but our own experience indicates that the prognosis is by no means as poor as this would indicate In the author s material many patients are alive and in relatively good condition or asymptomatic more than five years from the time of the first symptoms of the disease In Dean s large experience in South Africa there have been no deaths for a number of years Dean believes that with meticulous care very few patients will die In those cases in which only abdominal symptoms are present the outlook is distinctly better although these cases too may develop nervous system involvement at any time

Treatment From the standpoint of photosensitivity this is purely preventive consisting in protection from the light As stated ordinary window glass does not filter out the exciting light There is some evidence that vitamin B_1 is beneficial in reducing or eliminating photosensitivity in the hepatic cutanea tarda group but the writer s own experience with it has been indecisive

Splenectomy is of value in at least some cases of the erythropoietic type with splenomegaly and hemolytic anemia In one of our cases splenectomy has been followed by a complete symptomatic remission of the disease for a period of over eight years The anemia and photosensitivity have disappeared and the porphyrin excretion though still abnormal has decreased remarkably

Various methods of treatment have been advocated for the intermittent acute type but until recently all have been inconsistent or doubtful in their effectiveness The experience with chlorpromazine in the past three years indicates that it is much more valuable in the treatment of acute porphyria than any previous agent or method The great majority of patients obtain prompt relief of pain and nervous manifestations although established paralyses are unaffected Following the use of this drug in adequate dosage (up to 100 mg four times in twenty four hours) a remission of the disease has usually taken place At the same time it is clear that there is no direct effect on the disturbance of porphyrin metabolism as the excretion of porphobilinogen and porphyrins is unaltered by the drug and declines slowly only after the disappearance of symptoms It appears that chlorpromazine by allaying pain and nervousness interrupts a vicious cycle and permits the patient to go into remission This implies the presence of an important psychobiological factor which can scarcely be doubted on the basis of many observations

Other methods regarded as inferior to of investigators have stated that the administration of crude liver extract has re chlorpromazine nevertheless deserve brief mention Calcium given intravenously has been reported to be beneficial A number sulted in improvement The author s experience with both of these methods has been disappointing Demerol 50 to 100 mg given hypodermically has been of value in allaying pain although its effect has seldom lasted more than 4 hours In some instances it was clearly more effective than morphine probably because of its antispasmodic as well as analgesic effect

Tetraethylammonium chloride has been of definite value in reducing or eliminating pain One injection of 200 to 250 mg intravenously or 500 to 1000 mg of the chloride intramuscularly has provided complete relief for as long as twelve hours in some cases It is well to commence with a small dose as some cases are unduly sensitive and develop untoward hypotension In some cases a beneficial effect is entirely lacking Hexamethonium has been used in small amounts in two cases but in both was followed by a profound drop in blood pressure again indicating that there may be an unusual sensitivity in this disease

In a number of instances prompt remission has occurred following brief ACTH therapy In others no definite beneficial effect has been observed and in a few it has been thought that the effect was adverse actually hastening the patient s demise Present experience indicates that a brief trial of ACTH is warranted If no definite benefit has been observed within a four-day period it probably should not be continued

Barbiturates should not be used since there is definite evidence that they may precipitate or intensify the attacks There is evidence also that other chemicals including alcohol are precipitating factors in

such not regarded merely as a worsening of chronic uratic gouty arthritis

Patients whose first attack develops in middle or later life may never develop notable tophaceous deposits chronic gouty arthritis or significant renal involvement

Acute Gouty Arthritis *Typical Attack* Some patients recognize prodromes irritability melancholia nocturia polyuria vague muscular symptoms nausea dyspepsia or sometimes euphoria and a ravenous appetite Attacks begin any time day or night Those beginning at night if severe may awaken the patient in the early morning hours if mild they do not awaken the patient but are noted first when on awakening he puts his foot to the floor

In gout there is a gradient of articular vulnerability whereby distal joints—feet ankles hands wrists—are most commonly affected Knees and elbows are less vulnerable Shoulders and hips are rarely affected *clinically* except in severe or late gout Although the spine may acquire urate deposits acute or chronic gouty spondylitis is very rare Olecranon bursitis and tendinitis especially of Achilles tendon often occur

Attacks generally develop rapidly sometimes slowly Maximal disability may appear within twelve to thirty six hours Pain *may be mild or moderate but is often* severe—so excruciating that the weight of bedclothes or vibration of the bed is unbearable It is not always worse at night

The affected part is swollen and tender (Fig 63) often exquisitely so The skin may be bright or deep red sometimes dusky Inflammatory pitting edema may develop As swelling subsides there may be itching and desquamation Spontaneous recovery is sometimes slow but often rapid—within a few or several days In articular stage 1 clinical recovery is complete whether or not there are roentgenographic residues—a point of diagnostic importance "A person subject to gout has won the race at the Olympiac games during the interval of the disease" (Aretaeus)

Predisposing and Provocative Factors PREDISPOSING FACTORS Among men over thirty five years of age gouty arthritis is the commonest form of acute arthritis It should always be suspected when acute trauma is excluded Attacks come any time commonly in spring and fall Habitual (in contrast with acute) excesses of rich" or purine rich food and drink may condition patients to frequent attacks

PRECIPITATING FACTORS There are many provocatives of acute gouty arthritis trauma acute indiscretions as to food or alcoholic drinks psychic upsets chilling and hemorrhage certain therapeutic agents or procedures—liver extract mercurial diuretics ergotamine tartrate testosterone propionate roentgen therapy probenecid (Benemid) thiamine chloride (vitamin B_1) dehydrocholic acid (Decholin) high *fat or ketogenic diets penicillin sulfathiazole* transfusion purging bleeding possibly injections of pollen extract Contact with provocatives must be sought patients rarely recognize them

Attacks may be precipitated by minor trauma as from excessive walking long

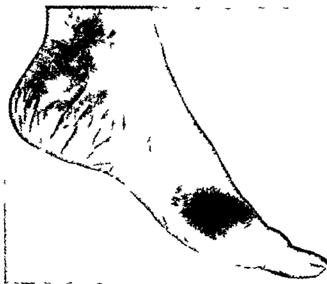


Fig 63 Acute gouty arthritis of great toe

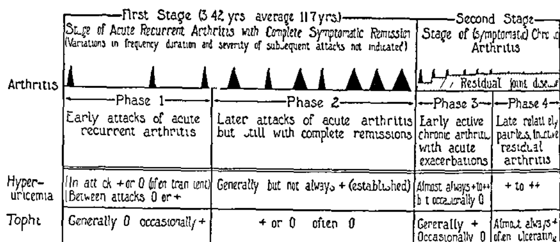


FIG 62 The basic pattern of gout and gouty arthritis (untreated) (P S Hench J Lab & Clin Med Vol 22)

often not until the menopause The serum uric acid level may be only intermittently *increased in the early phases Affected* subjects usually are entirely symptomless until the first attack of acute gouty arthritis appears which ordinarily does not occur for many years and indeed may not occur at all *In some instances however there may* be antecedent attacks of renal colic due to urate stones or gravel as an indication of the underlying metabolic disorder Very rarely in 2 per cent or less of cases detectable subcutaneous urate deposits (tophi) appear before any acute seizure

Stage of Acute Recurrent Arthritis With Complete Remissions The first attack of acute arthritis usually occurs suddenly lasts a few days or weeks then disappears completely It affects a great toe or with almost equal frequency ankle instep or knee *Sooner or later (a few months a* year or longer) there is another attack perhaps more severe or longer it also disappears completely Then attacks commonly increase in severity and frequency *coming* semiannually or oftener

Early attacks are generally monarticular afebrile and short (articular phase 1 Fig 62) Later attacks are often polyarticular longer and perhaps febrile (articular phase 2) Permanent roentgenologic changes may slowly develop despite which in this stage of the disease joints recover full symptomless function

During articular phases 1 and 2 attacks of acute olecranon bursitis may develop also with complete remissions in early attacks thereof there may be no palpable bursal *tophi* Acute bursitis may develop with or without acute arthritis

Stage of Chronic Gouty Arthritis From five to forty (average twelve) years after the first attack an important change may become apparent the onset of chronic *gouty arthritis the second form of articular* gout Sometimes when first discovered it appears to be the residue of an acute attack a joint no longer recovers completely But it may develop insidiously *without immediate reference to any previous attack*

Chronically affected joints may be subject to superimposed acute attacks (phase 3 Fig 62) But sometimes acute attacks (or "exacerbations") cease to recur (phase 4) *Chronic gouty arthritis* usually becomes polyarticular hands and feet may be misshapen by tophaceous deposits and deformities Tophi are usually present on the ears By now olecranon or prepatellar bursal walls may be chronically thickened from urate deposits and the tissue reactions thereto Chronic tophaceous "bursitis" may be *painless or mildly painful a process* apparently independent of the acute attacks of bursitis which may or may not continue to recur

Thus the pattern of classic gouty arthritis can be divided *clinically* into two stages comprising four phases (Fig 62) Although the stage of chronic gouty arthritis (or chronic bursitis) almost *always appears* after that of acute recurrent gouty arthritis these two clinical stages are not completely or necessarily interdependent indeed from the etiological or pathogenetic standpoint *acute gouty arthritis* and chronic gouty arthritis may be independent unrelated developments The pattern of acute recurrent gouty arthritis ordinarily *continues* basically unchanged after the development of chronic gouty arthritis If an acute attack is suddenly superimposed upon a *joint* which is the seat of chronic gouty arthritis this should be recognized and treated as

of the disease and increased values in 80 to 85 per cent (Hench Mason) The serum urate levels of normal and gouty patients fluctuate considerably from day to day In some gouty patients they fluctuate above and below the upper limit of normal at least early in the disease In others concentrations remain above normal but fluctuate without regard to attacks or to the use of nonuricosuric agents such as colchicine *Urinary* concentrations of urate (during periods without treatment) may fluctuate considerably even on a fixed diet

Visible or palpable *subcutaneous tophi* may develop at any stage occurring in about 30 to 50 per cent of cases They are rare in the prearthritic stage uncommon in articular phase 1 more frequent in phase 2 and almost always present in phases 3 and 4 when they may be multiple and ulcerating (Fig 64) They occur on the ears (Fig 65) and about olecranon bursae and peripheral joints A tophus is not a proved tophus until urate crystals have been recovered therefrom (Fig 66) Sometimes its identity should be certified by the murexide test or histological study

Areas of erosion of articular *bone* in gout represent replacement of bone by urates Osseous tophi are uncommon in articular phase 1 fairly common in phase 2 and more numerous and larger in phases 3 and 4 Areas of erosion (replacement of bone by nonurate debris) may occur in rheumatoid arthritis osteoarthritis or lupus pernio Hence erosions are not pathognomonic for gout but if large or numerous they are usually gouty

Sooner or later urate depositions affect certain renal tissues and constitute micro tophi in the kidneys On the distal side of the renal pelvic membrane urates may precipitate especially in acid urine coalesce and form urogenital gravel or stones Urate deposits may affect tendons but not muscular tissues *per se*

Except for exceedingly rare endocardial urate deposits the only certain examples of visceral gout are the urate accumulations and degenerative and inflammatory lesions in the kidney

About 10 to 20 per cent of gouty patients develop gouty nephritis or renal colic or both Hence suspect gout in cases of acute or chronic arthritis with renal colic or nephritis Ulcerating tophi may complicate late gout and lead to amputation of digits

The following are regarded as complications of gout by some as coincidental by others acute thrombophlebitis (in 3 5 per cent of cases) acute ocular inflammation hypertension (in 30 to 48 per cent) apoplexy coronary thrombosis or sclerosis

Additional Laboratory Data Erythrocyte sedimentation rates may be normal between attacks and in mild attacks but elevated sometimes markedly in severe acute attacks and in chronic gouty arthritis Serum concentrations of total cholesterol and esters are usually normal The excretion of 17 ketosteroids in the urine may be subnormal The levels of 17-corticoste



Fig 65 Two tophi on ear



Fig 66 Urate crystals from gouty tophus (× 435)

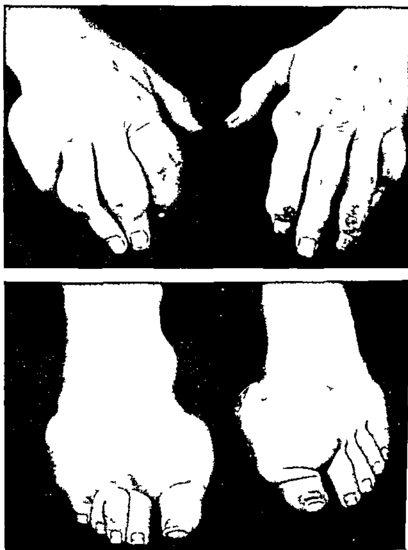


Fig 64 Severe chronic gouty arthritis with ulcerating tophi

motoring (pedaling) and sports True traumatic arthritis begins immediately after trauma the reaction is proportionate to the severity of trauma is confined to the traumatized region and is not relieved by colchicine characteristics of gout (history hyperuricemia tophi) are absent In post traumatic gouty arthritis the reaction is often delayed some hours is disproportionately severe after trivial trauma often progresses to other joints and is relieved by colchicine other characteristics of gout may be discoverable

Gouty arthritis is often provoked by acute dietary excesses associated with birth days weddings Thanksgiving New Years Day conventions vacations and lodge night Potent provocatives are hunting and fishing trips with their trauma and indiscretions around the camp fire (meats venison liquor) The hunter may return home with game gun and gout Episodic excesses of food and alcohol do not cause the gout *per se* any more than sugar causes diabetes but they may provoke symptomless gout and cause acute gouty arthritis Some attacks seems to be provoked by foods such as asparagus which are not rich in purines but may contain allergens

Surgical procedures commonly provoke acute gouty arthritis within the first seven postoperative days "In a case of acute postoperative arthritis suspect gout"

Accumulation of Urates The following data refer mainly to untreated gout The upper limits of normal values for serum urate in males are about 6 or 6 5 mg for females 5 or 5 5 mg per 100 ml According to certain writers once arthritis occurs hyperuricemia is present and persistent unless uricosuric agents are used But some observers have found *normal serum* urate concentrations in 15 to 20 per cent of gouty patients at various stages

mia develop? Three possibilities have been considered

1 Diminished Destruction of Urate Uricase has never been found in man but small amounts of urate are destroyed in the intestines by bacteria There is no convincing evidence that gouty persons are even less able than normal subjects to destroy urate

2 Deficient Excretion It was formerly believed that urinary urate excretion was often subnormal in gouty patients especially before acute attacks But some gouty patients during and between attacks excrete more urate than nongouty controls There is still considerable divergence of opinion as to the precise role of the kidney in the causation of hyperuricemia

3 Increased Production Biosynthesis of Uric Acid Uric acid in man is not solely derived from ingested purines or nucleoproteins but can be synthesized from simple carbon and nitrogen compounds present in carbohydrate protein and fat Feeding experiments with glycine (a precursor of uric acid) labeled with N^{15} or C^{14} have demonstrated overproduction of urate in some but not in all gouty subjects tested The evidence indicates that this excessive biosynthesis of urate from glycine ordinarily occurs by way of shunt pathways not involving incorporation into nucleic acids Thus while a metabolic abnormality leading to excessive biosynthesis of urate has been shown to occur in some patients with gout it is not possible as yet to generalize as to the cause of hyperuricemia in this disorder nor is it known what determines the localization and timing of the precipitation of urate in the tissues

Pathogenesis of Acute Gouty Arthritis It is often assumed that there is a direct connection between hyperuricemia urate deposits and acute articular attacks According to some writers an acute attack develops either when urate crystals are suddenly precipitated *de novo* (from supersaturated blood or extravascular fluid) into previously uncontaminated articular tissues or when urates already present in articular cartilage suddenly burst into the joint space But acute gouty arthritis is not a disease of the joint *space* it is an intense inflammation of various articular and periarticular *tissues* Actually it is not known when urates are deposited whether long before just before during or between attacks Massive infiltration of articular tissues by urate can be long present and painless Why would articular tissues remain long tolerant of their (sometimes extensive) urate infiltration and then suddenly react *acutely* either when some of this old urate is extruded into the joint *space* or when a new crop of crystals is precipitated in the articular tissues?

In considering what relationship (if any) exists between urates and acute gouty arthritis this summary should be noted 1 In gout the evolution of *hyperuricemia* does not necessarily parallel that of acute gouty arthritis 2 The pattern of acute gouty arthritis does not necessarily parallel that of subcutaneous or intra articular urate deposition Thus (*a*) one patient with a few attacks develops extensive tophaceous gout and chronic gouty arthritis whereas another with many attacks develops few tophi and no chronic arthritis (*b*) joints never affected acutely or chronically have been found at necropsy to be "whitewashed" with urates spinal joints do not escape urate deposition but acute gouty spondylitis almost never occurs and (*c*) *per contra* certain joints repeatedly attacked acutely have shown no *gross* urate deposits 3 Acute attacks are unrelated to any consistent change in the urate concentration of blood or urine serum and urinary urate do not change in any characteristic way just before or during attacks 4 The anti inflammatory and uricosuric effects of drugs useful in gout can be dissociated Thus (*a*) acute attacks are relieved by certain antiphlogistic agents (for example colchicine) which have no proved direct effect on urate metabolism or at least on urate excretion (*b*) acute attacks are *not* relieved by large uricosuric doses of probenecid and (*c*) pyrazinamide which markedly decreases urate excretion and increases serum urate does not provoke acute arthritis even in the gouty (Villa et al) and (*d*) the comparative effectiveness of cortisone corticotropin phenylbutazone and salicylates on attacks is *not* based on their relative uricosuric activity 5 The hyperuricemia of leukemia polycythemia and so forth usually remains symptomless 6 Urates *per se* are relatively innocuous Thus (*a*) peripheral tophi are usually painless (*b*) acute arthritis is not provoked when urates are injected intravenously into nongouty persons or into gouty patients during or between attacks and (*c*) urates injected subcutaneously are painless (Brown 1938) or are no more painful in the gouty than the nongouty (von Muller 1927) 7 Certain provocatives of acute gouty arthritis (such as purine free liver extracts Salyrgan Gynergen surgical operations) have little or no obvious connection

roids in the blood and urine are not far from normal (Villa *et al* 1958)

Cause of Death Patients with mild gout *and those responsive to prolonged therapy* commonly live their full span of years and die from something coincidental to their gout But there are many exceptions Common causes of death are uremia from gouty nephritis myocardial infarction and apoplexy

Roentgenographic Appearance The development of radiologically visible osseous tophi appears to be governed more by the gradient of articular vulnerability than by the general intensity of urate accumulation or the number and severity of attacks in any given joint Even in severe gout when many proximal or less distal joints are extensively affected by urates (as shown later by necropsy) areas of erosion rarely become *apparent* roentgenographically except in the feet and hands Such erosions appear occasionally in phase 1 (Fig 62) but commonly in phase 2 and thereafter Because the appearance of erosions is often delayed roentgenograms of joints are of limited diagnostic usefulness Periarticular thickening and nonspecific hypertrophic and destructive changes may involve joints sometimes in phase 1 but generally not until phase 2 and thereafter

Roentgenograms of the kidneys are also of limited value—urate stones cast no shadow

Etiology and Pathogenesis *Dissociation of Clinical Features* It is impossible to regard a single factor either an hereditary abnormality such as a gouty gene or one chemical substance such as urate as *the prime cause of all features of gout* The dominant clinical features are (1) the acute articular attacks and (2) the accumulation of urate (with the renal and *chronic* articular consequences thereof) But temporal relationships between the two are far from close and their pathogenetic relationships are quite uncertain Thus although the patterns of acute gouty arthritis and of urate accumulation often or commonly develop together at what might be called the same *general* rate the evolution of the one does not necessarily parallel that of the other or depend on it the two patterns are often dissociated If so the proximate causes of the two main features of gout may be quite separate and one is obliged to study separately the pathogenesis of each feature of the disease

Urate Accumulation Etiology and Pathogenesis Nature and Extent Isotopic techniques now permit more accurate measurement of urate accumulations by estimation of the "miscible pool" of urate (Stetten) When a small measured amount of isotopically labelled uric acid of known concentration or isotopic abundance is injected intravenously into man it mixes freely with the body s natural urates the degree of dilution depending chiefly on the total amount of urates momentarily present in the body Calculation of this dilution measures the miscible pool which is that quantity of urates in the body capable of mixing promptly with the injected urates and consequently of diluting the isotope Among normals the miscible pool varies between 700 and 1400 mg (average about 1 gm) and about 500 to 850 mg of old uric acid is replaced daily by newly formed (unlabelled) urate a turnover rate of 50 to 75 per cent Among the few gouty patients studied to date the pool has always been increased ranging between 1900 and 3400 mg in mild or moderate gout to over 30 000 mg in old severe untreated tophaceous gout In a patient with severe tophaceous gout the miscible urate pool after irregular treatment was 18 450 mg (15 times normal) rose after 4 5 months without treatment to 31 000 mg then fell to 2100 mg after the use of aspirin (2 to 4 gm daily) for three or four months (Benedict and co workers) ACTH cortisone or probenecid given for short periods reduced pools about 30 to 50 per cent and doubled the turnover rates by increasing renal clearance of urates and mobilizing the solid phase of miscible urates (Stetten)

Hereditary Factor in Hyperuricemia Of 449 members of 87 gouty families 21 per cent had clinical gout (arthritis and hyperuricemia or tophi) 15 per cent had symptomless hyperuricemia with no (other) signs of gout and 64 per cent had neither hyperuricemia nor active gout The conclusion is that *inherent susceptibility to gout* is transmitted by a single autosomal (that is not sex linked) dominant (gouty or hyperuricemic) gene with a low penetrance in both sexes (Talbott 1940 Smyth and co workers 1948 Stecher and coworkers 1949 1957) Most nonhyperuricemic relatives do not develop hyperuricemia in later life

Hyperuricemia usually does not appear until after puberty in males or near the menopause in females Nonhereditary factors related to sex renal function and normal androgenic activity are considered responsible for this change

Regardless of its ultimate cause by what mechanism does symptomless hyperurice

pletely Proper management and use of the drugs now available will retard or even reverse the process of urate accumulation prevent or heal the consequences thereof and also prevent or reduce the frequency and severity of acute attacks

Prophylaxis and Treatment Each phase and feature of gout requires its own treatment Measures for acute gouty arthritis are chiefly anti inflammatory those for interval gout (symptomless hyperuricemia and uratosis) are prophylactic and uricosuric those for chronic gouty arthritis are uricosuric and anti inflammatory those for gouty nephritis renal colic or tophaceous ulcers are of a special nature

Genetic Hyperuricemia of Gout Should every case of idiopathic hyperuricemia (not due to renal insufficiency blood dyscrasias and the like) be diagnosed and if so treated as pre arthritic gout? A presumptive diagnosis of pretophaceous pre articular gout is justified especially if the subject s family is gouty

How soon is prophylactic therapy indicated? It is postponed by some until the diagnosis is strengthened by the appearance of the first acute attack by others "until deposits of urates begin to declare themselves" "We would be doing the patient a disservice by starting him off on a lifetime of medication (Mason 1956) However it may be presumed that the deposition of urate in the tissues usually begins before the first attack of acute gouty arthritis perhaps years before and before tophi (subcutaneous osseous renal) are discernible Since the total morbidity in a given case of gout can be great and the mortality from fatal gouty nephritis is impressive prophylaxis should be instituted in the writer s opinion as soon as a diagnosis of gouty hyperuricemia (pretophaceous pre articular) is made certainly for a male member of a gouty family and for anyone with tophi and renal (uratic) colic The prophylactic regimen is fairly simple relatively inexpensive and safe

Acute Gouty Arthritis Most important for the treatment of acute gouty arthritis is its recognition few conditions respond more promptly to appropriate measures

For suspected attacks Patients who recognize some characteristic *nonarticular* prodrome or wonder whether mild articular twinges represent an impending attack may abort it by taking orally a few doses of colchicine (0 65 mg every one to two hours) It is wiser to do this for a possible false alarm than to let an attack become established

For recognized attacks Affected parts should be protected by rest preferably in bed sometimes in a light splint or by a light wooden or metal cradle Activity or weight bearing should be curtailed until pain and tenderness are gone otherwise an exacerbation may result Hot water or ice-cold compresses (every two to three hours) are often preferable to dry heat compresses of magnesium sulfate or lead lotion are sometimes prescribed

Colchicine given orally is generally the treatment of choice But it is commonly misapplied Necessary for success are (1) prompt administration (2) proper total dosage and (3) proper rate of dosage so as to provide a maximal antiarthritic effect with minimal gastrointestinal irritation If individual doses are too large or too closely spaced gastrointestinal irritation may develop before articular relief is obtained If doses are too small or too widely spaced effective blood concentrations are not obtained The sooner colchicine is given the smaller is the total dose required and the better the chance for relief without significant gastrointestinal irritation

Colchicine tablets each containing 0 5 or 0 65 mg are prescribed thus two tablets initially and one tablet usually every two (waking) hours sometimes every hour or every three hours depending on individual responsiveness severity of attacks and probable "nearness" to toxicity Colchicine is given until gastrointestinal symptoms (diarrhea sometimes nausea or vomiting) appear If a second course is required two or three days should intervene between courses or until diarrhea subsides Some patients having learned their toxic or "diarrheal dose (usually about six to fourteen tablets) may be able in subsequent attacks to obtain a therapeutic without a toxic effect by taking one or two less tablets to a course If not and if troublesome diarrhea impends or develops codeine or paregoric may prevent or control it Patients should always keep colchicine tablets handy at home at the place of business and especially in the suitcase for travel emergencies If attacks are treated promptly relief may begin within a few (twelve to twenty four hours) and be more or less complete within about twenty four to seventy two hours But in severe attacks or in patients not responsive to colchicine symptoms may persist for days or even weeks

Colchicine given intravenously usually produces quicker results often without toxicity This is indicated (1) whenever rapid

with urates or with marked changes in urate metabolism

All these data suggest strongly that acute gouty arthritis bears little or no (direct) relationship to urates But some precursor of urate might be responsible (Gutman)

Pathogenesis of Chronic Gouty Arthritis Tissue reactions to foreign matter (tophaceous deposits) in and around joints are considered responsible for the slow development of chronic gouty arthritis

From the foregoing it would appear that urates may have little or nothing to do with acute gouty arthritis but everything (more or less) to do with chronic gouty arthritis and that chronic gouty arthritis is not the end result of acute gouty arthritis or the sum total of acute attacks but that acute and chronic gouty arthritis may be quite unrelated to each other each having a different immediate cause and an independent (though sometimes parallel) evolution The same can be said for the relationship between acute gouty bursitis (for example olecranon) and chronic tophaceous bursal thickenings painless or painful

Pathogenesis of Gouty Nephritis Renal dysfunction is considered the cause of gout by some the result of gout by others Whether or not the undefined primary renal dysfunction" in the minds of the former is purely hypothetical or will some day be demonstrated it is not to be confused with the secondary renal dysfunction of gouty nephritis—a late characteristic of gout Intrarenal urate deposits presumably elicit a foreign body tissue reaction Varying degrees of dysfunction and destruction of renal units result superimposed thereon may be secondary infection Changes in the renal vasculature due to hypertension or to aging also play an important role

Pathogenesis of Vascular Complications The vascular lesions which may complicate severe or late gout bear no direct or obvious histopathological relationship to urate at least urate is practically never found therein The mechanism of their production is unknown

Adrenocortical Anterior Pituitary or Hypothalamic Dysfunction The hypothesis has been advanced that gout is an endocrine disease characterized by deficiency of *11 oxysteroids* that a chronic *relative* lack of 11 oxysteroids is characteristic of symptomless interval gout and that an even greater acute deficiency is related to acute attacks Since the adrenal cortices appear to be normally responsive in gout at least to exogenous ACTH the hypothetical dysfunction is said to involve either the anterior pituitary or more likely *the hypothalamus with sluggishness in* providing enough endogenous ACTH to satisfy the 11 oxysteroid requirements put upon the gouty patients by various stresses

No adrenocortical dysfunction during or between attacks has been found by other workers Colchicine does not increase adrenocortical activity Clinically recognized disorders of the anterior pituitary or adrenals either with hypofunction or hyperfunction are not associated with gout The urinary excretion of 17 ketosteroids is subnormal in most but not all cases of gout if this results from some adrenocortical or gonadal abnormality the nature and role of this abnormality are unknown There is as yet no indisputable evidence that pituitary or adrenocortical dysfunction plays a *primary* role in the pathogenesis of gout

Diagnosis The presence of any characteristic feature (podagra hyperuricemia peripheral tophi erosions) is of great diagnostic significance but the appearance of any one is often delayed until rather late in the disease The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases rarely or never in others Also hyperuricemia is usually present but one must not insist on its presence or that of podagra before diagnosing gout Usually a long rather than a short time elapses between "toe and tophus The pattern of recurrent arthritis with complete remissions is of itself so distinctive as to be almost pathognomonic although episodic rheumatoid arthritis and palindromic rheumatism must be excluded If diagnosis of any single attack is not helped by the history of previous attacks or if the initial attack is under consideration diagnosis is based on the characteristics of an attack as described including predisposing and provocative factors If an attack promptly responds to treatment (especially to colchicine specific for gout) the diagnosis of gout is justified even before the development of tophi

Prognosis Prognosis is best when gout is first manifest late in life poorest when symptoms begin before the age of twenty or twenty five years But estimation of prognosis is difficult In the untreated disease the frequency of attacks and the rate of urate accumulation may change capriciously 'The disease sticks to him till death wrote Aretaeus about 1600 years ago This is still true but now one can do much to control gout largely if not com

hours Treatment is seldom required after the fourth day (Freyberg and Smyth 1958) Large doses also have a moderate uricosuric effect (Gutman and Yu Kidd and co workers Kuzell and co workers)

Chief limitations are the toxic reactions which increase with length of treatment Toxic reactions affected 13 per cent of patients treated briefly for acute gouty arthritis and 32 per cent of those treated longer for chronic gouty arthritis reactions necessitated cessation of treatment in 4 and 8 per cent respectively Reactions include edema nausea epigastric pain morbilliform rash granulocytopenia and activation of peptic ulcer The drug is contraindicated whenever edema from cardiac renal or hepatic disease might develop

The old concept that attacks are related to urate retention and precipitation led to the use of uricosuric agents in acute gouty arthritis the rationale of which is by no means established Except for cortisone and ACTH (which appear to control attacks by anti inflammatory rather than by uricosuric action) uricosuric agents do not certainly prevent or control acute gouty arthritis Indeed acute attacks are sometimes precipitated by diuretic or uricosuric agents (salicylates cinchophen mersalyl [Salyrgan] probenecid) Despite its uricosuric effect probenecid (Benemid) is of no value for acute attacks indeed their incidence may increase during the early weeks of such therapy

There are no clear indications for a special diet during the attack of acute gouty arthritis A low purine diet a large intake of fluid and avoidance of alcohol are usually prescribed

Interval Treatment of Symptomless Gout Interval treatment aims to reduce the number and severity of attacks to retard or even reverse the process of urate accumulation and to prevent or postpone the late sometimes critical renal complications These intentions require the use not of a single remedy but of several measures combined

Preventive measures include the use of colchicine and the avoidance reduction or control of the psychic medicinal alcoholic dietary traumatic and surgical provocatives of acute gouty arthritis The more or less continuous use of *colchicine* in nonirritating doses is of prophylactic value (Cohen 1936 Gutman and Yu 1952) For mild cases (less than one attack yearly) one tablet (0 5 mg) is given once daily for three or more days a week for moderate cases (more than one attack yearly) 0 5 mg once daily throughout the week for severe cases two or three tablets are given daily more or less continuously (Talbott 1958) Sometimes this made the difference between virtual incapacitation and relatively normal activity Patients have taken colchicine daily for 5 to 10 years without discomfort or drug tolerance (Kersley and co workers 1950 Talbott 1942 1957) Most patients continue to tolerate about 1 3 to 2 6 mg colchicine daily occasionally less

Postoperative gouty attacks can generally be prevented by use of either a high carbohydrate purine free diet and salicylates for five days before and five days after operation (Hench) or colchicine (0 5 mg three times a day if given orally or 1 5 mg once a day if given intravenously) for at least three days before and after operation (Kersley and co workers 1950 Talbott) or ACTH (with or without colchicine orally) for two to three days before and after operation (Coste and co workers)

Diet Opinion on the rationale of diets in gout is undergoing revision The chief aim of dietary management in recent years usually has been not so much to relieve or to prevent acute attacks as to assist in counteracting hyperuricemia and the deposition of urate in the tissues Ingested purines are a rich source of urate ingested protein contributes significantly to urate production a diet high in fat decreases renal excretion of urate carbohydrates foster urate excretion but excesses produce obesity to be avoided Taking these considerations into account the diet commonly recommended for interval gout is low in purines and fats adequate in proteins (50 to 75 gm daily) especially in purine free proteins and generous but not excessive in carbohydrates In such a diet would be cereals grain products eggs cheese milk fruits and nonleguminous vegetables to which could be added one serving of meat fish or fowl five days a week (Gutman and Yu Hench) Patients with a life time disease would hardly accept a more restrictive diet moreover since man can synthesize urate not only from purines but also from purine free proteins (as the labeled glycine experiments demonstrate) carbohydrates and fats there are definite limits to the effectiveness of any diet however restrictive in reducing urate biosynthesis

Deficiencies in protein iron and vitamin B must be avoided generally gout diets should be reinforced with an approved vitamin preparation for example one hexa

relief is particularly desirable (2) when good results from colchicine given orally are complicated by marked gastrointestinal irritation (3) for acute postoperative attacks (4) for attacks unresponsive to colchicine given orally perhaps belatedly In dividual doses have varied from 0 65 mg one to three times daily to 3 mg once daily the latter is the most effective (Graham and Roberts Ward) Patients often require only one or two injections occasionally more Relief may begin within an hour or two of the first injection is often notable within six to twelve hours and is more or less complete within eighteen to thirty six hours (Ward) Gastrointestinal irritation rarely develops from one or two injections (1 5 to 3 mg each eight to twenty four hours apart) but may be mild or moderate if several injections are required Colchicine is very irritating if injected outside the vein

Corticotropin (ACTH) (aqueous) in sufficient doses rapidly controls most acute attacks even those unresponsive to colchicine If enough ACTH or cortisone is given long enough attacks are usually controlled without relapses Misnamed withdrawal flares are simply relapses of attacks caused by premature discontinuence of temporarily adequate treatment or discontinuance of doses which were never adequate and are not due to ACTH induced pituitary adrenocortical insufficiency as has been stated

If aqueous ACTH is used alone (that is without colchicine) recommended doses are for the first day 100 to 200 mg (in divided doses) depending on the attack s severity for the next three days or so 80 to 120 mg daily Thereafter *even though symptoms are more or less completely controlled* use of ACTH should be continued though in progressively smaller daily doses for four to eight more days total treatment lasting about a week or two Colchicine resistant attacks or attacks which develop despite prophylactic use of colchicine between attacks often require larger doses of ACTH than otherwise From adequate doses relief begins often within four hours of the first dose may be marked (75 to 90 per cent relief) within twenty four hours and complete within twenty four to seventy two hours Even so the attack though symptomatically suppressed has generally not run its full course until a week or two have passed It is advantageous to give colchicine in doses of 1 mg daily by mouth as the dose of ACTH is lowered and to continue this after administration of ACTH is terminated in order to prevent exacerbations of acute gouty symptoms

Attacks are controlled with long acting ACTH gels given intramuscularly once daily (total doses comparable to those of aqueous ACTH) or with ACTH given by *intravenous* infusion (20 to 30 U S P units in 500 ml of fluid over a period of six to eight hours)

According to some writers *cortisone* is inferior to ACTH—indeed relatively useless Consequently relatively few patients have been treated with cortisone given intramuscularly and even fewer with cortisone hydrocortisone or prednisone tablets given orally despite great practical advantages Unsatisfactory results have been largely from underdosage or premature discontinuance if enough cortisone is given long enough most attacks are controlled promptly Rapid relief without relapses has resulted from cortisone given occasionally for only three to four days but generally for one to three weeks Successful doses have been either 200 to 300 mg daily for the first three to four days then progressively smaller doses for one to two weeks more or 100 mg daily for about two to three weeks

The combined use of cortisone and colchicine has been effective 100 mg of *cortisone in divided doses and 2 mg of* colchicine (0 65 mg three times daily) for a week or more Relapses due to premature discontinuance of cortisone (used alone) have been controlled either by giving cortisone a few more days or by giving cortisone plus colchicine

Prednisone has given very satisfactory results in daily doses of 25 mg or more less satisfactory results were obtained with smaller doses

Attacks have been controlled promptly by injections (often one only) of 25 to 50 mg of *hydrocortisone acetate into gouty* joints or bursae (Hollander)

Phenylbutazone (Butazolidin) is also effective when given intramuscularly 0 6 to 1 0 gm (generally the latter) once daily or orally 100 to 800 (generally 400 to 600) mg daily in four divided doses *The oral* preparation is convenient and effective particularly when given in a schedule which provides 600 mg as a first (priming) dose and 200 mg at two- to four hour intervals thereafter until a response is obtained Inflammation usually lessens within a few hours after the first dose pain is controlled generally within twenty four hours the attack may disappear within seventy two

hours Treatment is seldom required after the fourth day (Freyberg and Smyth 1958) Large doses also have a moderate uricosuric effect (Gutman and Yu Kidd and co-workers Kuzell and co-workers)

Chief limitations are the toxic reactions which increase with length of treatment Toxic reactions affected 13 per cent of patients treated briefly for acute gouty arthritis and 32 per cent of those treated longer for chronic gouty arthritis reactions necessitated cessation of treatment in 4 and 8 per cent respectively Reactions include edema nausea epigastric pain morbilliform rash granulocytopenia and activation of peptic ulcer The drug is contraindicated whenever edema from cardiac renal or hepatic disease might develop

The old concept that attacks are related to urate retention and precipitation led to the use of uricosuric agents in acute gouty arthritis the rationale of which is by no means established Except for cortisone and ACTH (which appear to control attacks by anti inflammatory rather than by uricosuric action) uricosuric agents do not certainly prevent or control acute gouty arthritis Indeed acute attacks are sometimes precipitated by diuretic or uricosuric agents (salicylates cinchophen mersalyl [Salyrgan] probenecid) Despite its uricosuric effect probenecid (Benemid) is of no value for acute attacks indeed their incidence may increase during the early weeks of such therapy

There are no clear indications for a special diet during the attack of acute gouty arthritis A low purine diet a large intake of fluid and avoidance of alcohol are usually prescribed

Interval Treatment of Symptomless Gout Interval treatment aims to reduce the number and severity of attacks to retard or even reverse the process of urate accumulation and to prevent or postpone the late sometimes critical renal "complications" These intentions require the use not of a single remedy but of several measures combined

Preventive measures include the use of colchicine and the avoidance reduction or control of the psychic medicinal alcoholic dietary traumatic and surgical provocatives of acute gouty arthritis The more or less continuous use of *colchicine* in nonirritating doses is of prophylactic value (Cohen 1936 Gutman and Yu 1952) For mild cases (less than one attack yearly) one tablet (0 5 mg) is given once daily for three or more days a week for moderate cases (more than one attack yearly) 0 5 mg once daily throughout the week for severe cases two or three tablets are given daily more or less continuously (Talbott 1958) Sometimes this made the difference between virtual incapacitation and relatively normal activity Patients have taken colchicine daily for 5 to 10 years without discomfort or drug tolerance (Kersley and co workers 1950 Talbott 1942 1957) Most patients continue to tolerate about 1 3 to 2 6 mg colchicine daily occasionally less

Postoperative gouty attacks can generally be prevented by use of either a high-carbohydrate purine free diet and salicylates for five days before and five days after operation (Hench) or colchicine (0 5 mg three times a day if given orally or 1 5 mg once a day if given intravenously) for at least three days before and after operation (Kersley and co workers 1950 Talbott) or ACTH (with or without colchicine orally) for two to three days before and after operation (Coste and co workers)

Diet Opinion on the rationale of diets in gout is undergoing revision The chief aim of dietary management in recent years usually has been not so much to relieve or to prevent acute attacks as to assist in counteracting hyperuricemia and the deposition of urate in the tissues Ingested purines are a rich source of urate ingested protein contributes significantly to urate production a diet high in fat decreases renal excretion of urate carbohydrates foster urate excretion but excesses produce obesity to be avoided Taking these considerations into account the diet commonly recommended for interval gout is low in purines and fats adequate in proteins (50 to 75 gm daily) especially in purine free proteins and generous but not excessive in carbohydrates In such a diet would be cereals grain products eggs cheese milk fruits and nonleguminous vegetables to which could be added one serving of meat fish or fowl five days a week (Gutman and Yu Hench) Patients with a life time disease would hardly accept a more restrictive diet moreover since man can synthesize urate not only from purines but also from purine free proteins (as the labeled glycine experiments demonstrate) carbohydrates and fats there are definite limits to the effectiveness of any diet however restrictive in reducing urate biosynthesis

Deficiencies in protein iron and vitamin B must be avoided generally gout diets should be reinforced with an approved vitamin preparation for example one hexa

vitamin capsule U S P every one or two days Normal weight should be maintained and obesity avoided or corrected Coffee and tea are permissible

Fortunately control or reversal of uratosis can now be accomplished more effectively by uricosuric agents than by diets Hence there is a growing leniency with respect to the eating habits of gouty persons Nevertheless it is still logical to decrease the purine load on the kidneys and other tissues by avoidance of purine rich foods and excesses of proteins and fats Of course any food or alcoholic drink which (regardless of purine content) seems repeatedly to provoke attacks should be avoided Temperance rather than abstinence from alcohol is commonly recommended

For prolonged uricosuria *probenecid* a benzoic acid derivative currently is considered the best agent (Gutman and Yu Talbott) Serum urate is decreased and excretion of urinary urate is notably increased by suppression of tubular resorption For uricosuria probenecid (Benemid) (2 gm daily) is much more effective than neocinchophen (3 gm daily) or aspirin in small doses (2 to 3 gm daily) and more effective than aspirin 5 gm daily but less effective than aspirin or sodium salicylate plus sodium bicarbonate 5 gm of each daily

Doses of probenecid are 0 5 to 2 gm or more daily Most toxic reactions are minor they include nausea anorexia constipation and rash Allergic reactions sometimes develop One severe reaction (headache muscular aching pruritus dyspnea nausea vomiting chill fever) developed after ten days of therapy (2 0 gm daily) and recurred later after a single test dose of 0 125 gm (Kloempken and Montgomery 1952) Larger doses (2 0 gm daily) are rarely needed unless renal insufficiency or extensive tophaceous deposits are present Patients should receive also a liberal fluid intake and sodium bicarbonate (about 2 to 5 gm daily) to prevent renal gravel Probenecid and salicylates should not be given concurrently each counteracts the uricosuric effect of the other (Gutman and Yu 1951 Pascale and co workers) ACTH does not interfere with probenecid

Probenecid tends to provoke gouty arthritis during the first weeks of treatment (in 18 per cent of cases) thereafter attacks may become fewer than before treatment Vigorous uricosuria from overzealous dosage together with insufficient fluids and alkalis may produce a momentary "flash colic" a true renal colic or urate crystalluria and hematuria

Marked uricosuria is produced by *aspirin* or *sodium salicylate* in daily (divided) doses of 4 to 6 gm or more but not by daily doses of less than 3 or 4 gm (Hanzlik 1927 Graham 1920 1933) Salicylates inhibit tubular resorption of urate The uricosuric effect of salicylates may be enhanced by the concurrent use of sodium bicarbonate (Gutman 1950) Prolonged use of aspirin or sodium salicylate (about 1 5 gm four times a day) and sodium bicarbonate (1 3 gm four times a day) may be recommended for those few who tolerate such amounts without salicylism Sodium bicarbonate is given (1) to increase the solubility of urinary urates so as to prevent the spontaneous or therapeutically induced formation of uratic calculi or (2) to enhance salicylate uricosuria Sodium bicarbonate occasionally produces gastrointestinal symptoms erroneously ascribed to the uricosuric agent Then an alternate method of urinary alkalinization is necessary

The prolonged use of the cortisones corticotropins cinchophen and phenylbutazone as uricosuric agents is not recommended

Chronic Gouty Arthritis Joints "white washed with urates can be symptomless Where and whether chronic inflammation appears depends on at least two factors tissue receptivity to urate deposition and tissue vascularity Urate deposits are not found in tissues of the central nervous system or in muscle tissue *per se* (except at tendinous attachments) Chronic granulomatous inflammation develops around urate deposits in vascularized tissues (synovia bone marrow) but not in avascular tissues (hyaline and fibrous cartilage) (Collins 1951) But in articular cartilage degeneration may develop *Per contra* the characteristic pathology of acute gouty arthritis is an acute cellular inflammation with or without urate crystals or any chronic foreign body cell reaction

For the prevention and treatment of chronic uratic gouty arthritis measures must be directed against two known factors the uratosis and the resulting chronic inflammation present or impending The prevention of future urate deposits and the slow (partial) mobilization and excretion of some of those already present are accomplished to some degree at least by avoidance of foods rich in purine and continual administration of probenecid or other uricosuric agent Prolonged use of a uri

cosuric agent has reduced the size of subcutaneous tophi healed tophaceous ulcers and fostered the sclerotic repair of osseous tophi (Gutman and Yu 1952) To the extent that uricosuric agents can reduce the articular uratosis which may provoke chronic inflammation and degeneration they can relieve chronic uratic arthritis slowly and indirectly But the supplementary use of anti inflammatory agents is usually or often indicated

After symptomatic chronic gouty arthritis has developed the patient is still subject to recurring attacks of acute gouty arthritis The nature and proper treatment of the latter are usually recognized when an attack suddenly involves joints unaffected by chronic gouty arthritis But when upon the latter is superimposed a sudden acute attack which is mistaken for an exacerbation of the chronic uratic arthritis anti inflammatory measures may be neglected in favor of rest physical therapy probenecid and so forth It is important therefore to distinguish between chronic (uratic) gouty arthritis (type of inflammation and symptoms) and exacerbations thereof and a case of chronic uratic arthritis complicated temporarily by a superimposed *acute* gouty (nonuratic) arthritis

Chronic (uratic) gouty arthritis (including true exacerbations thereof) appears *not* to be relieved by colchicine But it may be amenable to the prolonged use of phenylbutazone daily maintenance doses of 100 to 200 mg (de Seze et al 1958) Intra articular injections of phenylbutazone 400 mg gave "striking results when an acute inflammatory episode supervened in chronic gouty arthritis of knees" Whatever part of a supposed "flare" of chronic uratic arthritis is rather promptly relieved by the usual anti inflammatory measures (colchicine intravenously or orally ACTH cortisone or prednisone hydrocortisone intra articularly phenylbutazone orally intramuscularly or intra articularly) is that part representing an inflammatory reaction to the nonuratic noncrystalline (rather than to the uratic) irritant of articular gout It is not unreasonable to suppose that in severe cases the two types of inflammation combine to produce a chronically painful joint Except for colchicine (useful only against acute nonuratic inflammation) and probenecid (useful only against uratosis) the antigout (anti inflammatory) medicinals appear to be nonspecific

Gouty Nephritis Prevention and Treatment Prolonged administration of a uricosuric agent is useful for the prevention and treatment of uratic renal lesions as are also abundant intake of fluids especially water and constant alkalinization of the urine Special measures are required for pyelonephritis renal insufficiency or uremia

Vascular Accidents Prevention and Treatment One can only speculate on the mechanism or agent responsible for vascular complications For their prevention the physician must rely on the general regimen already outlined

Treatment of Gross or Ulcerating Tophi Special treatment is required for some tophi such as painful ones on weight bearing surfaces large ones which prevent use of regular shoes or gloves or some in which fistulous ulcers are present or impending Prolonged therapeutic uricosuria may heal draining sinuses If tophi remain troublesome they should be excised The removal of a small tophus under local anesthesia can be done usually without a postoperative flare But when one or more large tophi are to be excised and if general anesthesia is used one should institute prior to tophectomy a regimen to prevent acute postoperative (that is post tophectomy) gouty arthritis

Results of Therapy Although gout is not yet curable its important manifestations are now largely controllable if treatment is planned carefully applied early and with appropriate modifications continued resolutely Available is impressive clinical and photographic evidence that the progress of hyperuricemia and uratosis can be not only retarded but kept "in reverse with normalization of uricemia prevention of new and reduction in the size of old subcutaneous tophi nonsurgical healing of tophaceous ulcers and the prevention or lessening of symptom producing chronic arthritis

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Diabetes Insipidus

Definition Diabetes insipidus is the clinical state resulting from a deficiency of antidiuretic hormone (vasopressin) Its principal features are the persistent excretion of large volumes of a dilute but otherwise normal urine unrelenting thirst and compensatory polydipsia There is no intrinsic renal disease and replacement therapy usually relieves the symptoms promptly

Incidence and Etiology This relatively rare condition can be inherited or acquired The hereditary type which accounts for about 2 per cent of all cases is transmitted as a dominant character with poor penetrance in the female that is more commonly in males and with skipped generations Acquired diabetes insipidus may result from any lesion which damages or destroys any of the essential structures of the hypothalamico neurohypophyseal system Approximately one third of the cases are attributable to primary or metastatic intracranial neoplasms and one third to a wide variety of lesions (traumatic post operative infectious vascular granulomatous etc) one third are without apparent cause or demonstrable pathological findings

Physiology Increasing evidence supports the view that both the elaboration and release of antidiuretic hormone are effected by neurons of the supraoptic and paraventricular nuclei of the hypothalamus Scharrer and his colleagues maintain that the hormone originates in the hypothalamic nuclei as neurosecretory material which migrates along the axons to be stored in their terminations in the neurohypophysis

The rate of release of antidiuretic hormone is modified by many influences such as (1) remote activities in the central nervous system resulting from emotion pain or exposure to cold (2) the osmoreceptors described by Verney which are exquisitely sensitive to changes in the osmolarity of blood perfusing the internal carotid arteries (3) a variety of chemical agents which suppress (alcohol) or promote the release of hormone (nicotine morphine phenobarbital ferritin BAL etc)

Although the exact site and mode of action of vasopressin remain conjectural it is generally accepted that the hormone causes an increased reabsorption of water from tubular urine without altering either glomerular filtration or the excretion of electrolytes There is no evidence that vasopressin influences the reabsorption of water in the proximal convoluted tubule Recent studies on frog skin indicate that the hormone is capable of opening or widening "pores" in the membrane to facilitate the passive movement of water along osmotic gradients A similar mechanism has been suggested by some investigators to account for its action in the renal tubule According to this view vasopressin is believed to increase the passive reabsorption of water which follows the active transport of electrolytes (*cf* section on Renal Physiology and Tests of Renal Function)

The urine volume in diabetes insipidus is dependent in part on the quantity of solutes such as urea and electrolytes which must be excreted Inability to elaborate a urine of more than very limited concentration necessitates an increasing excretion of water with an increasing solute load Coincident destruction of the anterior lobe of the hypophysis lessens the severity of diabetes insipidus by decreasing the solute load presented to the tubules This occurs as the result of both a reduction in glomerular filtration rate and a decreased dietary intake of protein and salts

Diagnosis In general the diagnosis of true diabetes insipidus can be established with certainty only when the following criteria are fulfilled (1) a history of persistent polydipsia and polyuria with daily urine volumes of 5 to 20 liters (2) a consistently low urinary specific gravity which cannot be raised above 1 010 by the withholding of fluids (3) a failure to evoke significant antidiuresis by stimuli such as hypertonic saline or nicotine which promote the release of hormone from a functional neurohypophyseal system and (4) the administration of 0 1 unit of Pitressin causes antidiuresis and urine concentration Water deprivation which results in an increase in the serum sodium concentration has been largely abandoned as a routine test procedure because of the intolerable thirst and occasionally dangerous dehydration which may result In the test devised by Hickey and Hare the intravenous infusion of hypertonic saline (0 25 ml of 2 5 per cent sodium chloride per kg of body weight per minute for 45 minutes) after the establishment of water diuresis induces antidiuresis in normal subjects but not in patients with diabetes insipidus It is a valuable test when carefully performed

but its use is contraindicated in patients with coexistent cardiovascular disease The inhaling of 1 to 3 cigarettes and the subcutaneous injection of 1 to 3 mg of nicotine tartrate have also been employed as stimuli to provoke antidiuresis in the hydrated subject In interpreting the results of this test account should be taken of the patient s smoking habits and it should be appreciated that transitory antidiuresis may occur even in diabetes insipidus if nicotine produces an abrupt drop in blood pressure and glomerular filtration rate Parenteral nicotine should not be administered to patients with coronary insufficiency It is important to recognize that a relatively mild diabetes insipidus occurs occasionally from a partial deficiency of antidiuretic hormone In such instances both the hypertonic saline and nicotine tests may cause antidiuresis and elevation of the urine specific gravity but not to the degree observed in normal subjects

Patients with primary psychogenic polydipsia present the commonest problem in differential diagnosis Diabetes insipidus can usually be excluded by a history of gradually increasing polydipsia and polyuria often by the relief of symptoms with placebo preparations and by normal responses to the tests already discussed

Roussak Oleesky and others have described a diabetes insipidus like syndrome occurring in the course of chronic renal disease and have designated this condition "water losing nephritis" Williams and Henry have introduced the term nephrogenic diabetes insipidus to indicate a familial probably sex linked disorder occurring in males in which polydipsia and polyuria begin in infancy In addition diabetes insipidus like states have been observed in potassium deficiency and following excessive doses of desoxycorticosterone acetate or cortisone In all of the foregoing syndromes the polyuria is largely unaffected by the administration of Pitressin and diagnosis should not be difficult if these possibilities are considered

Treatment Replacement therapy is available in three types of preparations desiccated posterior pituitary powder a soluble aqueous extract and Pitressin tannate in oil The nasal insufflation of 10 to 50 mg of the powder several times each day usually provides effective control of the symptoms This is a convenient and economical form of therapy but nasal irritation frequently prevents its continued use The aqueous extract is commonly employed in diagnostic procedures but in replacement therapy it must be injected subcutaneously at intervals of four to twelve hours and its rapid absorption from the injection site may produce unpleasant musculotropic effects on the gastrointestinal tract The sparingly soluble Pitressin tannate suspended in vegetable oil provides effective therapy when injected subcutaneously in doses of 0 2 to 0 4 ml every two to three days This is currently the regimen most widely employed Occasional individuals exhibit allergic reactions to the posterior pituitary preparations It should be emphasized that water intoxication is a potential complication of parenteral administration whether diagnostic or therapeutic Although the patient with diabetes insipidus usually decreases his fluid intake as polyuria is controlled the psychogenic water drinker may not

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Diabetes Mellitus

Definition The disease known as diabetes mellitus is a disorder of carbohydrate metabolism characterized by hyperglycemia and glycosuria This disorder is associated with a disturbance of the normal insulin mechanism When carbohydrate metabolism becomes seriously deranged there are readily demonstrable abnormalities of protein and fat metabolism The latter may give rise to ketosis acidosis coma and death The disturbance in the insulin mechanism is believed to be due in some cases to a decrease in the elaboration of insulin by the pancreas and in others it probably results from an increase in insulin requirement by the tissue cells to maintain normal carbohydrate metabolism

History The growth of our knowledge of diabetes mellitus demonstrates admirably a pattern of scien

tific development which has led repeatedly to significant medical progress Clinical description of the disease came first Aretaeus appropriately described a melting down of the flesh and limbs to urine The first and crude demonstration of the chemical nature of the disorder is ascribed to Susruta who in the fifth century described honey urine as confirmed by Thomas Willis 1200 years later and to Dobson who in the eighteenth century demonstrated the presence of sugar in the urine The third significant step was the physiological demonstration by von Mering and Minkowski in 1889 that extirpation of the dog s pancreas was followed by the development of a condition strikingly similar to diabetes in man Hyperglycemia glycosuria and ketonuria appeared and when glucose was fed it was excreted quantitatively in the urine After this histopathological studies in man by Opie in 1900 showed some degree of correlation between degeneration of islet tissue in the pancreas and the presence of diabetes This was supported by the experiments of Ssobolew who in 1902 demonstrated that degeneration of the tryptic portion of the pancreas did not result in diabetes

The final step which appeared to establish the proof that diabetes mellitus arises from intrinsic disease of the pancreas was accomplished by the classic studies of Banting a surgeon and Best then a medical student in 1921 They prepared an extract of the islet tissue of the pancreas when the tryptic portion had degenerated after ligation of the pancreatic ducts This extract depressed the blood sugar of the diabetic dog as had extracts prepared by Zuelzer in 1907 and others at later dates from whole pancreatic tissue These extracts were unpredictable in terms of toxicity but preparations safe for clinical use were soon prepared by alcoholic extraction procedures developed by J B Collip a member of Banting s group With the development of insulin which corrected the disturbances of carbohydrate metabolism in diabetic dogs and humans it was believed that all the riddles of diabetes mellitus had been solved

Further study has shaken this confidence and suggests that diabetes mellitus may be more complex than it appeared to be immediately after the discovery of insulin and that intrinsic disease of the pancreas may not in most cases be the primary cause after all These misgivings which arose on the basis of clinical observations in a variety of endocrine disorders received impressive support in the startling experiments of Houssay This investigator in 1930 found that the severe diabetes resulting from pancreatectomy in the dog was greatly ameliorated if the pituitary gland was subsequently extirpated Long and Lukens later demonstrated the same improvement when instead of the pituitary the adrenal glands were removed in pancreatectomized cats It appeared therefore that the elaboration of insulin was essential for the control of hyperglycemia glycosuria and ketosis only when the adrenal or pituitary glands were present More recently total pancreatectomy has been performed in man and it appears that whereas this procedure results in the development of diabetes the intensity of the process as judged by insulin requirements is considerably less than in patients with the spontaneously occurring disease in whom the pancreas at autopsy may show only minor change Thus the simple hypothesis which appeared both satisfactory and adequate four decades ago yields to uncertainty and complexity and constitutes a challenge to future investigators

Incidence Surveys of Wilkerson and others indicate a prevalence rate of diabetes of between 1 4 and 1 7 per cent Thus there are probably in excess of 2 000 000 overt cases in the United States The potential reservoir of diabetes is considerably in excess of this since a number of studies show that many persons with borderline postprandial hyperglycemia in subsequent years develop the typical disease

Since the advent of insulin the total mortality from diabetes is reported to have increased the death rate in the period from 1935 to 1940 alone increased from 22 5 to 26 6 per 100 000 This can undoubtedly be ascribed in part to the general increase in life expectancy which increases the number of people who acquire diabetes in later life and also to the greater accuracy of the diagnosis of diabetes In contrast to the reported increase in diabetic deaths in persons more than fifty years of age is the sharp decrease in the diabetic death rate in the earlier decades This can be credited wholly to insulin therapy Whereas patients formerly died at an early age they now live to become victims of the arteriosclerotic period of life

Age Diabetes may develop at any age but the curve of incidence reaches its peak in the fifth and sixth decades According to Joslin approximately 50 per cent of all diabetes occurs between the ages of forty and sixty years Only 5 per cent occurs in the first decade and 3 per cent in the eighth

Sex Between the ages of forty and seventy years diabetes is significantly more common in women than in men the ratio being approximately 3 to 2 In earlier life there appears to be a slight preponderance in males It is possible that the high incidence in women more than forty is related to the high incidence of obesity in this group

Etiology It must be emphasized at the outset that the etiology of diabetes mellitus is undetermined in the vast majority of patients However it is apparent from experimental studies and clinical observation that a number of factors may disturb the normal insulin mechanism and thereby induce the hyperglycemia and glycosuria typical of diabetes For this reason it might be more accurate to consider the etiologies of diabetes

The capacity to metabolize carbohydrate as well as other substances must be considered a fundamental process inherent in most if not all tissue cells This property probably constitutes a heritage from our unicellular ancestors What part primary disturbances of the intrinsic enzyme sys

tems concerned with these oxidative processes may play in diabetes mellitus is still obscure It is known however that certain endocrine glands through the elaboration of their respective hormones are able to influence profoundly the metabolism of various foodstuffs therefore the relations of these glands to the origin of diabetes must be considered

The Pancreas Insulin is elaborated by the beta cells of the islands of Langerhans in the pancreas It is therefore to be expected that total pancreatectomy will terminate insulin production thus giving rise to severe and rapidly fatal diabetes This is true in the dog but in other species the diabetes induced by pancreatectomy is much less intense

Total pancreatectomy in man has been performed on a number of occasions Diabetes appears promptly after this procedure but in contrast to that in the dog is not of great severity Patients may require 25 to 50 units of insulin daily with a liberal ingestion of carbohydrate This dosage of insulin as already stated is considerably less than that required by many patients suffering from diabetes of spontaneous origin Hence it is probable that factors other than a decrease in liberation of insulin from beta cells of the islets contribute to the severity of diabetes in many patients For example in certain cases primary abnormalities in the cellular enzyme systems may increase the demand for insulin In others it is obviously related to antagonistic action of one or more hormones a concept to be discussed later In a few instances it is probably referable to an antigen antibody reaction which inactivates insulin as evidenced by the binding of I^{131} labelled insulin to fractions of serum globulins Also fluorescin tagged insulin antibody is specifically bound to beta cells in some animal species

Diabetes has been induced by chemical agents which have a necrotizing effect upon the beta cells of the pancreas but permit the alpha cells to remain intact One of these *alloxan* a pyrimidine derivative causes permanent and severe diabetes in twenty four to forty-eight hours after injection in all species so far studied This form of diabetes is readily controlled by insulin as is that following pancreatectomy The administration of massive doses of alloxan to a few patients with terminal generalized carcinoma and to those with cancer of the islands of Langerhans has had no significant effect Like alloxan dehydroascorbic acid induces diabetes in rats and rabbits

It is established that a protein *glucagon* is elaborated by pancreatic tissue other than the beta cells and has anti insulin activity Glucagon is presumed by many to be secreted by the alpha cells Its elaboration according to Young is enhanced by hypoglycemia and by pituitary growth hormones Observations of Dorner and Stahl and others indicate that alpha cells disappear in the hypophysectomized dog The action of glucagon is short lived and the hyperglycemia caused by it is believed by Sutherland to result from increased hepatic glycogenolysis resulting from enhanced phosphorylase activity which in turn results from the formation of a dinucleotide in hepatic mitrochondria The action of glucagon resembles that of epinephrine its role in the etiology of diabetes is not known Evidence for peripheral action is not convincing

Haist and Best observed that the insulin content of the pancreas of the normal rat could be sharply reduced either through starvation or by the administration of insulin to the normally fed animal These procedures were not accompanied by any histological change in the pancreas Haist and Best inferred from their studies that resting the pancreas relieved the "strain imposed by hyperglycemia and is beneficial The observations of Haist and Best showing a decrease in insulin content of the pancreas with rest furnish at least a partial explanation for what is termed starvation diabetes encountered in man and certain animals It has been repeatedly observed that after starvation or a low carbohydrate diet the administration of glucose is followed temporarily by hyperglycemia of an abnormal degree and duration often associated with glycosuria Transient diabetes has also been observed following the surgical relief of recurrent hypoglycemia due to islet cell tumors In this case also it appears that time is required for the islet cells to regain their normal function after prolonged relative inactivity Wrenshall and Best find practically no insulin in the pancreas of juvenile diabetics but glands of adult diabetics yield 25 to 30 per cent of the normal

Diabetes in man may occur in association with a variety of diseases of the pancreas In *hemochromatosis* it is not unusual to have associated diabetes which some believe to be due to extensive siderosis and fibrosis of islet tissue Mild diabetes

appears in some patients with *carcinoma* of the pancreas and may result from destruction of islet tissue as may also be true in the case of large pancreatic *cysts* Acute *hemorrhagic pancreatitis* is not infrequently associated with hyperglycemia and glycosuria and permanent diabetes has been reported following recovery from pancreatitis *Trauma* of the pancreas has been purported to be a cause of diabetes but this view is not established on firm grounds

The Pituitary It has long been known that diabetes mellitus is frequently found in association with acromegaly It was therefore natural to suspect that hormones of the anterior lobe of the pituitary gland were in some way capable of disturbing carbohydrate metabolism It remained however for Young (1937) to demonstrate that typical diabetes could be permanently established in dogs by the administration of a potent extract of the anterior lobe of the pituitary (APE) when injections were continued daily for about four weeks Histological study of the pancreas of these animals showed lesions characteristically found in many patients with diabetes

These important sudies of Young left in doubt the question whether anterior pituitary extract exerted a direct effect upon beta cells of the islets similar to that observed following alloxan Best Haist and Campbell showed that the administration of a diet low in carbohydrate or the administration of insulin inhibited the diabetogenic effect of anterior pituitary extract as well as the development of histological changes in the pancreas The basis for the development of Young s diabetes was finally established through the ingenious experiments of Lukens and Dohan They induced "Young s diabetes in partially pancreatectomized cats in which hydropic degeneration of beta cells persists for some months before fibrosis occurs These investigators found that after the injections of anterior pituitary extract were discontinued and before fibrosis of islet tissue occurred the diabetes which had been established was curable Cure could be effected in any one of three ways each of which abolished hyperglycemia first by reduction in carbohydrate intake second by the administration of insulin and third by the administration of phlorizin In other words the permanent diabetes induced by APE appears to result in the main from exhaustion of the beta cells by interference with carbohydrate utilization and long continued hyperglycemia Young and others believe it also acts through stimulation of glucagon Of importance is the further observation of Lukens and Dohan who have shown that permanent diabetes with characteristic pancreatic changes can also be induced in normal cats through the maintenance of hyperglycemia for a period of ten days by the intraperitoneal injection of glucose alone

How many fractions of anterior pituitary extract may play a part in the genesis of diabetes is not yet established Pure growth hormone or somatotropin (STH) unquestionably has the capacity to induce permanent diabetes in dogs and cats but only in partially pancreatectomized rats Also Cori and Bornstein have found a lipoprotein in beef pituitary which inhibits the glucokinase reaction and thus may prove to be diabetogenic The observations of Ladd and of White concerning the onset of diabetes in children suggest that among others the growth hormone may be implicated Thus Ladd found that 30 out of 34 children carefully studied were overgrown or overweight or both at the onset of their disease White reports that 86 per cent of children with diabetes were definitely overheight within three months prior to the onset of their disease Obesity was not a significant factor in White s patients Furthermore there are numerous reports of women who have given birth to oversized infants months or years before the onset of diabetes in themselves suggesting hypersecretion of growth hormone in the mother during pregnancy The role of ACTH in the genesis of human diabetes appears to be a minor one since a vast number of individuals have been given this hormone in amounts sufficient to induce prolonged and intense hypercorticism with only infrequent initiation of transient diabetes However the enhancement of diabetes by ACTH is not to be questioned

The Adrenal Glands Lukens and Long first showed that extirpation of the adrenal glands ameliorated pancreatic diabetes in dogs and cats just as Houssay found a beneficial effect from hypophysectomy With these observations the importance of the adrenal cortex in the genesis of disturbances of carbohydrate metabolism became firmly established Ingle has been able to induce heavy glycosuria in intact rats by intensive administration of adrenal 11-oxysteroids thus further emphasizing the importance of certain adrenal steroids in their capacity to act either directly or indirectly as an anti insulin The increase

in glycosuria induced by 11-oxysteroids in the rat is ascribed by Stetten and Ingle to an increase in gluconeogenesis

Himsworth points out that patients with diabetes (and probably nondiabetic persons) can be divided into insulin resistant and insulin susceptible groups The whole implication of this generalization is not known but it is probable that either pituitary or adrenal cortical hormones or both are significantly concerned with at least some of the variations in insulin resistance In support of this view is the fact that the diabetes occurring with acromegaly or Cushing s syndrome may be mild as judged by the degree of glycosuria and hyperglycemia but the dosage of insulin required to relieve it is reputed to be inordinately great On the other hand in the absence of adrenal cortical hormones or in pituitary insufficiency even intense diabetes may be incredibly sensitive to minute amounts of insulin Of interest is the observation of Vallance Owen and Lukens that an insulin inhibitor appears in the plasma of pancreatectomized cats *only* following four days of *combined* administration of growth hormone and adrenal oxysteroids The antagonist resides in one of the globulin fractions of the plasma

It remains to be determined how frequently excessive secretion of anterior pituitary extract or certain adrenal cortical steroids with their antagonistic behavior toward insulin activity may be of importance in the development of diabetes in man

Whereas *epinephrine* is responsible for transient hyperglycemia as a result of increased glycogenolysis there is no convincing evidence suggesting that the adrenal medulla plays any part in the initation of diabetes mellitus

The Thyroid Gland Wilder reported an incidence of 3 2 per cent of frank diabetes mellitus in a series of patients with hyperthyroidism Diabetes occurred more than three times as often in Wilder s patients with toxic nodular goiter as in patients with exophthalmic goiter probably because of the higher incidence of nodular goiter in older age groups in whom diabetes is most prevalent Experience dictates that overactivity of the thyroid gland should always be suspected in diabetic who are difficult to regulate and require large doses of insulin since it is well established that hyperthyroidism intensifies diabetes mellitus However it has not been possible to establish permanent diabetes in animals by thyroid administration in contrast to the effect of the administration of anterior pituitary extract

Obesity Among 1000 diabetics reported by Joslin 77 per cent were definitely overweight and only 8 per cent were below the normal zone Among 252 diabetics between the ages of 51 and 60 only 2 were below normal weight prior to the onset of their disease It is a striking fact that the correlation between obesity and diabetes occurs only in the adult group and particularly among older adults

A majority of older obese diabetic patients lose evidence of a disturbance in carbohydrate metabolism with reduction in weight Thus it appears that the capacity of these patients to metabolize carbohydrate tends to be impaired only in association with a food intake sufficiently in excess of normal to establish obesity When their caloric intake is reduced to a level commensurate with the maintenance of normal weight diabetes tends to disappear

It seems possible that the strain" on the pancreas to elaborate insulin essential for oxidation of excessive carbohydrate or possibly for fat storage may lead in time to diabetes in those people with a genic predisposition to the disease In this connection it is of interest to note that diabetes appears in mice exhibiting hereditary obesity Also Long and his co workers have shown that rats rendered obese by hyperalimentation after hypothalamic injury may in time develop diabetes From a practical standpoint the essential fact is that a relationship between obesity and diabetes is found in more than 50 per cent of persons with diabetes

Heredity A family history of diabetes can be obtained in at least 25 per cent of patients Furthermore the incidence of diabetes in both of identical twins is approximately 70 per cent in contrast to less than 10 per cent in twins derived from separate ova These facts in addition to studies of White and Pincus and also of Wilder indicate that the predisposition to diabetes is inherited as a Mendelian recessive which is not sex linked *It is not known whether the genic defect finds its expression at the hormonal level in the form of imbalances or at a more fundamental level involving defects in enzymatic processes* Be that as it may the implication of White s and Pincus studies is that 100 per cent of the offspring of two diabetic parents will develop the disease—assuming the etiology of diabetes in both parents is the same

There is a mass of evidence offered in

support of different etiologies for juvenile diabetes and the diabetes of older obese persons To be mentioned are the acute onset in the juveniles and typically mild symptoms in the obese *the lack of fat in* the liver in juvenile diabetics and classic fatty liver of the obese *the lack of insulin* in the pancreas of *the juvenile* diabetic and its presence in the obese adult the relative insulin sensitivity in the juveniles and comparative resistance in the obese also the possible overactivity of the pituitary gland in juvenile diabetics as suggested by their oversize *Nevertheless it must be remembered that persons who develop their diabetes when they are fat and elderly may have children who develop classic juvenile diabetes* This suggests a common genic defect but different precipitating factors in the susceptibles

Infection One of the most characteristic features of diabetes is the fact that infection may intensify the disease process and may increase enormously the demand for insulin This is particularly true of febrile diseases but is also true of infections as trivial as the common cold The mechanism by which activation of diabetes takes place is wholly obscure It is not known whether infectious processes decrease the formation of insulin They do however stimulate liberation of ACTH with increased secretion of steroids of the adrenal gland

Diabetes often develops after an acute infectious disease but it seems improbable that the infection initiates diabetes in these patients More probable is the explanation that these patients are latent diabetics and that infection merely brings the disease to light

Race It is a generally accepted fact that diabetes is more common among Jews than among other people This high incidence is almost entirely limited to elderly Jews and is in all likelihood associated with a high incidence of obesity

Disturbances of the Nervous System Certain authors have emphasized that the incidence of diabetes is highest among persons whose occupations are associated with nerve strain and great responsibility but it must be recognized that a sedentary existence associated with consequent obesity in this group is probably of greater significance The appearance of glycosuria following sudden emotional upsets or cerebral trauma is well established and was commented upon by Willis in 1679 but this is transitory in nature and is probably dependent upon sympathetic discharge of epinephrine It seems certain that "psychic trauma" can temporarily increase the severity of established diabetes and consequently increase insulin requirements This becomes a point of practical importance in the management of the disease

Whatever the etiology of diabetes the disease can be looked upon from a standpoint of practical management as a disorder in which the amount of endogenous insulin available is inadequate to meet the metabolic demands

Physiology The ability of a physician to understand the disturbances responsible for the clinical picture of diabetes mellitus and likewise his ability to treat the disease intelligently and successfully are dependent upon the knowledge of the metabolic processes involved It is essential in gaining this background of information to contrast certain aspects of normal metabolism with the deviations encountered in diabetes

Carbohydrate Metabolism Normal carbohydrate metabolism proceeds along a number of pathways as indicated in Figure 62 A portion of the glucose from which carbohydrate metabolism originates is converted into glycogen in the liver and muscles The remaining glucose is broken down by glycolysis to lactate and pyruvate and possibly to other 3-carbon fragments without the interposition of glycogen formation likewise shown in Figure 67 The phosphorylation of glucose to glucose 6 phosphate is the first and essential step both for its conversion to glycogen and its degradation to smaller fragments Pyruvate is decarboxylated to form acetyl CoA and concomitantly the reduction of diphosphopyridine nucleotide to DPNH occurs Acetyl CoA then condenses with oxaloacetic acid to be oxidized to CO and water via the tricarboxylic acid cycle When carbohydrate is broken down to Acetyl CoA in excess of energy requirements two molecules of acetyl CoA condense to form aceto acetyl CoA This enters the fatty acid spiral and on each turn condensation with additional acetyl CoA takes place lengthening the chain by two carbon atoms Thus for example in eight turns of the spiral stearic acid is formed and ultimately fat stores at the periphery are increased

Essentially all carbohydrate is broken down in the gut into the three hexoses glucose fructose and galactose before being absorbed It is generally accepted that these sugars are actively transported through the gut wall and that they do not traverse the mucosa of the small intestine by simple diffusion

Three Sources of Body Glucose Obvi

ously the largest amount normally comes from the food a second source is liver glycogen and a third source is that derived from gluconeogenesis

Liver glycogen is derived from glucose either ingested or synthesized in the body e g from lactic or pyruvic acid elaborated to a large extent in the muscles It turns out from studies on the rat by Stetten that the total amount of glycogen stored in the normally fed animal in twenty four hours is equivalent to only about 3 per cent of the total glucose metabolized Hence stored glycogen appears to be almost insignificant as a source of glucose for metabolic requirements in the normal animal This statement does not detract however from the vital importance of liver glycogen as an emergency stabilizing factor for the blood sugar level The glycogen of the liver as well as that in the muscles derived from glucose appears as a product elaborated by a series of reactions involving the phosphorylation of glucose These reactions are reversible except for the initial phosphorylation of glucose but it is worthy of note that the final step in the degradation of liver glycogen to glucose is accomplished by a specific phosphatase present in the liver but not in muscles consequently no free glucose is formed from muscle glycogen

In addition to glucose absorbed from the gut and to that derived from liver by glycogen glucose may be synthesized from a variety of building blocks within the body This synthesis is termed *gluconeogenesis* Gluconeogenesis appears to take place primarily in the liver from 2 to 3-carbon fragments which appear in the course of the metabolism of protein fat and carbohydrate Included in these are certain amino acids from protein (*e g* alanine) glycerol from fat lactate and pyruvate from glucose and probably many other substances The amount of glucose made available by gluconeogenesis in the normal rat according to Stetten is approximately ten times that derived from glycogen The importance of this process in body economy is apparent

The Normal Fate of Glucose in the Body As stated before only about 3 per cent of the glucose metabolized by the normal rat is to be accounted for by glycogen formation Of the remaining 97 per cent Stetten has shown that 30 per cent *i e* ten times as much as goes to glycogen is converted to fatty acids after breakdown to acetyl coenzyme A The portion of glucose not converted to glycogen or fatty acid (about 70 per cent of the total) after being split to lactate pyruvate and other 3-carbon fragments is either oxidized (chiefly in the muscles) by means of the tricarboxylic acid cycle to carbon dioxide and water or is made available for amino acid and ultimately protein synthesis

Carbohydrate Metabolism in Diabetes The major defect in carbohydrate metabolism in diabetes mellitus is due to a decrease in the utilization of glucose It seems probable that gluconeogenesis from protein is significantly increased by 11-oxysteroids of adrenal origin Studies of Stetten have demonstrated conclusively that the amount of extra glucose found (gluconeogenesis) in phlorizin diabetes in which the loss of sugar is dependent solely upon a renal lesion is just as great as it is in the truly diabetic animal (alloxan poisoned) in which the loss of glucose is due to a disturbance in the insulin mechanism In other words *there is no more "overproduction" of glucose in alloxan diabetes than in renal glycosuria induced with phlorizin* It appears at the present time that "under utilization" of glucose results from the summation of three defects (*vide* Figs 67 and 68) first a decrease in oxidation of glucose and a decrease in its utilization in

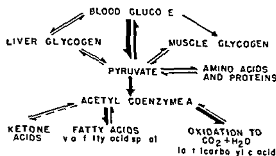


Fig 67 Diagram of normal carbohydrate metabolism (Thickness of arrows indicates possible magnitude of the reactions)

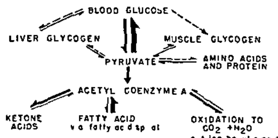


Fig 68 Diagram of carbohydrate metabolism in diabetes mellitus (Thickness of arrows indicates possible magnitude of the reactions)

amino acid and protein synthesis and some increase in gluconeogenesis second a decrease in fatty acid formation from glucose *to about one twentieth of the normal* thus making this nonmetabolized glucose also available for urinary excretion and third a decrease in glycogen storage in the liver and muscles which however contributes only slightly to the total amount of glucose *excreted over any considerable period of* time

It must be emphasized that whereas the capacity to oxidize glucose and the ability to convert glucose to glycogen may be seriously impaired in diabetes these functions *contrary to earlier thought* are not completely interrupted It may well be that the oxidation of glucose which does continue in the brain and probably in other tissues in diabetes is independent of insulin action and is akin to that in unicellular organisms *which utilize carbohydrate without a* pancreas This is also suggested by the fact that the depancreatized animal is capable of increasing the utilization of glucose in response to muscular work This appears to result from an increase in the transport of glucose into cells similar to that induced by insulin

Glucose may be oxidized after phosphorylation by a pathway known as the "hexose monophosphate shunt This pentose pathway does not follow the steps of the conventional Embden Meyerhof anaerobic glycolysis Its importance has not been entirely clarified but it appears to be involved at least in the formation of ribose for nucleic acid synthesis and for the elaboration of TPNH Activity of the pentose pathway is reduced in severe diabetes

Insulin This hormone of the islands of Langerhans is a single protein the biological activity of which is dependent upon the integrity of the disulfide bridges between cysteine residues in adjacent polypep*tide chains The monomeric insulin mole*cuel has a molecular weight of 5734 and it exists in micelles of molecular weight of about 48 000

The mechanism of action of insulin is not firmly established and two views continue to prevail Levine and Goldstein have presented impressive evidence favoring the idea that insulin acts by enhancing the penetration of glucose into the cell and that in the diabetic animal glucose fails to be utilized because it is incapable of entering the cells where it is normally phosphorylated and then utilized *Cori has shown* that this effect of insulin is not specific for hexoses but applies also to certain pentoses Cori and Cori maintain that the defect in diabetes results from an inhibition of phosphorylation of glucose to glucose 6 phosphate by a factor in the pituitary gland This may be growth hormone They believe that insulin counteracts this pituitary inhibition of glucokinase The utilization of glucose appears to be dependent upon a binding of insulin to the muscle Chaikoff has shown as has Miller that *in vitro* or *in vivo* fructose in contrast to glucose is utilized normally by tissues of the diabetic organism Levine suggests that this is because insulin is not needed for the penetra*tion of fructose into cells With the alterna*tive hypothesis it would be assumed that the fructokinase reaction is intact whereas the glucokinase reaction is disturbed in the diabetic The balance of evidence at present favors the view of Levine In the ab*sence of insulin there is some reduction* in oxidative phosphorylation (in the cat) and also an increase in glucose 6 phosphatase in the liver It seems possible that these changes are secondary to the failure of glucose penetration into cells rather than being *specific defects*

Regardless of the mechanism of action of insulin its over all effects are readily demonstrable in the diabetic animal The reactions which appear to benefit at least indirectly from the administration of insulin are indicated in Figure 69 Here it will be seen that insulin enhances the normal breakdown of glucose to pyruvate which is ultimately oxidized to carbon dioxide and water and which also serves as a stepping stone in the conversion of glucose to fatty acids Furthermore insulin appears to aid indirectly in the synthesis of certain amino acids and their incorporation into body protein By virtue of increasing glucose oxidation insulin decreases gluconeogenesis in the diabetic and thereby decreases the loss of nitrogen from *the body The increase in glucose* utilization following insulin injection similarly decreases the need for mobilization and oxidation of fat in the diabetic It appears that both fat storage and protein synthesis are dependent upon the oxidation of glucose In the absence of insulin protein synthesis induced by growth hormone is minimal Insulin also greatly increases glycogen storage in the liver and to a less extent in striated muscle in diabetes It actually decreases glycogen storage in cardiac muscle and kidney

In the normal animal insulin tends to decrease glycogen storage in the liver This

appears to result from an increase in glycogen storage or glucose utilization in striated muscle which results in a decrease in the blood sugar level This in turn results in glycolysis in the liver to reestablish the level The action of insulin at the periphery was demonstrated by its augmentation of the arteriovenous difference in blood sugar in an extremity in the early studies of Cori and Cori

A number of *types of insulin* are now available for clinical use All are derived from either hog or beef pancreas and all have the same basic actions on carbohydrate metabolism The preparations of insulin in use include *regular insulin crystalline insulin globin insulin protamine zinc insulin NPH insulin* and *zinc insulin mixtures* The chief difference in these modifications of insulin is in the time of action Thus in the fasting diabetic regular and crystalline insulin exert their effect on blood sugar for about six to eight hours with a peak effect at about three to four hours Globin insulin is active for about twenty to twenty four hours with maximal action at eight hours NPH or isophane insulin about equivalent to 2 1 mixture of regular and protamine zinc insulin exerts action for twenty four to twenty eight hours with maximal action also at about eight hours Protamine zinc insulin (PZI) may have activity persisting in excess of thirty hours with a peak effect between twelve and twenty four hours The Danish zinc and insulin suspensions (IZS) vary in their duration of action from eighteen to ninety six hours Commercial lente insulin is an admixture of semilente and ultralente zinc insulins and has a time action curve like that of isophane insulin The duration of action of any insulin varies in different persons depending on rates of absorption and other unknown factors

The *adrenal glands* exert important influences on carbohydrate metabolism *Epinephrine* when administered to the well nourished animal characteristically raises the blood sugar as a result of increasing the breakdown of liver glycogen to glucose When liver glycogen stores are depleted epinephrine appears to decrease muscle glycogen similarly with the liberation of lactic acid which is transported to the liver and resynthesized to glycogen or glucose The *adrenal cortex* as mentioned under Etiology is capable of causing profound changes in carbohydrate metabolism The 11 oxysteroids induce glycosuria and an increase in nitrogen excretion in normal animals and they intensify already-existing diabetes The mechanism of action of these steroids has not been established but they are known to inhibit the synthesis of certain proteins and enhance strikingly gluconeogenesis from proteins Cori believes they enhance inhibition of phosphorylation of glucose by pituitary hormones

As stated above growth hormone particularly in association with insulin is effective in increasing nitrogen storage by augmenting protein synthesis It is also diabetogenic as discussed elsewhere

The effect of the *thyroid* hormones as mentioned before intensifies glycosuria in the diabetic and causes transient glycosuria in normal persons This effect appears to result primarily from the fact that thyroid substance increases the rate of absorption of glucose so that the hreshold for excretion is readily exceeded It also increases glycogen breakdown

Blood Sugar The concentration of glucose in the blood at any given time is the resultant of forces tending to remove glu close to the tissues for utilization and forces leading to the synthesis of glucose or to an increase in its flow to the blood stream as indicated by the arrows in Figure 67 The most important factor quantitatively determining the height of the blood glucose level is obviously the glucose absorbed from the gut The normal fasting blood sugar level is 80 to 120 mg per 100 ml of which about 20 mg is not glucose and is accounted for by other reducing substances After the ingestion of a liberal amount of carbohydrate the level rises normally to about 150 mg per 100 ml in thirty to sixty minutes and returns approximately to the fasting level in the course of two hours

In order to maintain the normal fasting blood sugar level the pancreas must liberate the proper amount of insulin This control mechanism is generally believed to be regulated by vagal stimulation and the concentration of glucose in the blood Thus when the blood sugar level begins to rise

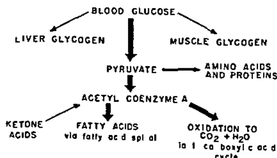


Fig 69 Diagram of processes apparently enhanced by insulin in the diabetic

the islet cells are stimulated to elaborate more insulin When the level tends to fall insulin formation is diminished and the liberation of epinephrine and glucagon is believed to stimulate glycogenolysis in the liver which restores the blood sugar level The part played by anterior pituitary ex tract and certain adrenal cortical steroids in the maintenance of the normal blood sugar level is undoubtedly also of great importance

When the blood sugar level is in excess *of about 170 mg per 100 ml glycosuria* appears Under these conditions the renal tubules are unable to reabsorb all the glu cose present in glomerular filtrate In a number of older diabetics the normal renal threshold is raised and the urine remains sugar free even when the blood glucose level is greater than 300 mg per 100 ml Possibly this elevation of threshold can in some way be correlated with capillary glomerulosclerosis which is common in this group of patients and results from a de crease in filtration and in some instances an increase in tubular reabsorption

Fat Metabolism The storage of neutral fat occurs chiefly in the subcutaneous depots This fat is derived normally from that ingested and from fatty acids derived from glucose as described under Carbo hydrate Metabolism The liver which is intimately involved in fat metabolism as well as in carbohydrate metabolism nor mally contains 2 to 4 per cent of fat Concentration of fat in excess of 10 per cent may appear in the liver however under a great array of circumstances in cluding obesity pregnancy starvation phlorizin diabetes and in elderly obese but not in juvenile diabetics Diets containing large amounts of fat biotin or cystine or diets deficient in methionine choline or betaine also give rise to an increase in the fat content of the liver as do chloro form and other liver poisons

The mechanisms by which *fat is mobi lized* from the peripheral tissues to the liver are not understood However a sub stance in the anterior pituitary adipo kinin is capable of inducing this migra tion of fat The importance of this pituitary stimulus for fat mobilization in the variety of conditions under which liver fat is increased is not known and the way in which it affects mobilization is also obscure

The total lipid concentration of the nor mal plasma is from 500 to 600 mg per *100 ml* Approximately one half of this is in the form of neutral fat and fatty acid and the remainder is composed of choles terol and its esters and phospholipid When the rate of mobilization is greatly increased as in uncontrolled diabetes complicated with severe ketosis the concentration of blood lipid may be enormously increased in one of the writer s patients it reached 25 per cent Unesterified fatty acids (UFA) are present in normal plasma in minute amounts but have an enormous turnover rate UFA decrease normally in plasma with administration of glucose or insulin *and increase in diabetes particularly* with impending ketosis Gordon has shown that epinephrine *in vitro* increases UFA release from adipose tissue and insulin *in vitro* depresses this process The full implication of these observations is not yet apparent

The *oxidation of fat* begins in the liver (except for a small increment in the kid neys and other tissues) and proceeds by stepwise degradation down the fatty acid spiral the length of the molecule being shortened by two carbon atoms on each turn with the formation of one molecule *of acetyl CoA perhaps by a process* the reverse of that for fatty acid synthesis out lined in the Section on Carbohydrate Metab olism In the complete degradation of fatty acids the acetyl CoA formed is oxidized to CO and water as mentioned above In the severe diabetic there does not appear *to be any difficulty with fat degradation* which is actually greatly increased On the other hand fatty acid synthesis comes al most to a standstill The large quantities of acetyl CoA not oxidized are diverted into the synthesis of ketone acids This diver sion has been variously ascribed to a dimin ished supply of reduced pyridine nucleo tides or oxaloacetate resulting from failure of carbohydrate metabolism Convincing evidence for either of these hypotheses is lacking

Ketone bodies are rapidly transported from the liver to other tissues notably the muscles where they serve both in the nor mal and the diabetic as a source of energy and are ultimately oxidized to carbon di oxide and water This utilization is so com plete that under normal conditions only traces of ketone bodies appear in the blood and urine

Ketosis and Acidosis In the course of uncontrolled diabetes glycosuria increases in intensity and is accompanied by a large rise in the urinary excretion of nitrogen due to an increase in gluconeogenesis (the gluconeogenesis appears to be at least in part due to the inability to store protein normally in the absence of insulin*)* *Soon*

there follows a great increase in the catabolism of fat The rate of breakdown of fat to ketone bodies in itself a normal process is far in excess of the rate at which acetoacetic and beta hydroxybutyric acids can be utilized by muscles and other tissues Consequently the ketone bodies increase in the blood at times reaching levels of 200 mg or more per 100 ml This ketonemia is associated with urinary ketone body excretion which often exceeds 60 gm a day

Ketosis develops also in other disorders in which adequate amounts of glucose are not available as in the course of starvation or in phlorizin poisoning It also appears when the diet contains fat in excess of about 4 gm for each gram of glucose available as such or that derived from protein (about 58 per cent) It seems certain that glucose oxidation is essential both for the storage of fat and the synthesis of body protein When oxidation of glucose is sharply reduced in diabetes as a result of an inadequate supply of insulin or in starvation because of an inadequate supply of glucose then mobilization and breakdown of fat with varying degrees of ketone formation transpire by the routes indicated above Also in the absence of glucose oxidation negative nitrogen balance ensues because of failure of protein synthesis and because of gluconeogenesis from amino acids

One of the many unresolved problems concerning the mechanism of ketosis is the unpredictability with which it appears For example one of two wholly similar diabetics may in the course of twenty four hours after the withdrawal of insulin exhibit serious ketosis in association with heavy glycosuria The other under apparently identical circumstances and with the same glycosuria will develop essentially no ketonemia or ketonuria despite persisting glycosuria and nitrogen loss It may be stated as a generalization that juvenile (insulin deficient) diabetics are prone to severe ketosis and that obese elderly (insulin resistant) diabetics are less subject to ketosis but there are exceptions

Because two of the three ketone bodies are acids their continued elaboration leads to *disturbances of acid base equilibrium* Their accumulation in the blood plasma reduces the bicarbonate content and ultimately causes severe acidosis Both acetoacetic and beta hydroxybutyric acids are relatively strong acids and whereas they are in part excreted as such a much larger part is excreted in association with cations Some of this is furnished by the ammonia mechanism but there is also serious depletion of fixed cations including sodium potassium and calcium as acidosis progresses Moreover Atchley Richards and the writer showed that the loss of fixed cations in severe diabetes actually begins coincidentally with the development of heavy glycosuria and before ketosis occurs This loss of cations is associated with the loss of intracellular and extracellular water as well as with the breakdown of cells as judged by nitrogen loss The general problem of acidosis is dealt with elsewhere in this volume

The accumulation of beta hydroxybutyric acid in the body is relatively harmless except for its effect upon acid base equilibrium On the other hand acetoacetic acid and acetone are distinctly toxic and their accumulation depresses the central nervous system It seems probable that a considerable part of the picture of diabetic coma may properly be ascribed to intoxication by these ketone bodies Kety has demonstrated a 40 per cent reduction in cerebral utilization of oxygen in diabetic coma and ascribes it in part to the acidosis and more significantly to the ketosis and possibly other factors

Caloric Requirements Age sex surface area physical activity state of nutrition fever thyroid activity and probably many other factors influence energy requirements Consequently to attempt to set down the number of calories required by any person to maintain a given weight is not in most instances helpful In general sedentary adults require in the neighborhood of 30 calories per kilogram the requirements of children are greater and those of the aged tend to be less The deviations from these generalizations are however great and the only practical procedure to be followed in establishing caloric requirements is that of trial and error using body weight as an index It should be noted that the caloric requirements of the diabetic do not differ from those of the normal

The protein requirements are also variable and are goverened more or less by the same factors which influence the total caloric needs The amount of carbohydrate in the diet however has a significant effect upon the protein intake essential to maintain nitrogen equilibrium An intake of 100 to 150 gm of carbohydrate daily cuts down nitrogen loss in starvation appreciably With increase in carbohydrate beyond this amount Butler has shown that additional nitrogen sparing action of car

bohydrate is inappreciable at least in normal young adults

Morbid Anatomy The commonest histological lesions in diabetes mellitus are found in the pancreas It is interesting to note however that in the meticulous studies of postmortem material by Cecil and others more than 10 per cent of the cases failed to reveal any pancreatic lesions *In the cases in which changes are encountered in the pancreas* no one distinctive lesion is uniformly present in the islets In some cases there appears to be a reduction in the total number of islets without other lesions demonstrable In others hydropic degeneration of the beta cells has been noted The most frequently encountered lesions are hyaline degeneration and sclerosis of the islands of Langerhans The lesions observed may be secondary to an abnormality of carbohydrate metabolism *originating outside the pancreas* as in "Young s diabetes or as in cats maintained hyperglycemic by the prolonged administration of glucose intraperitoneally Local destructive disease of the pancreas including diffuse pancreatitis extensive tumors and large cysts may be the cause of diabetes Also hemochromatosis with intensive infiltration of the pancreas with hemosiderin and ceroid is often associated with diabetes

The kidney is frequently the site of a variety of lesions in diabetes mellitus These include pyelonephritis capillary glomerulosclerosis and necrotizing papillitis discussed in the section on Complications

Sherlock has demonstrated by liver biopsy striking increase in deposition of fat in the older relatively resistant obese diabetics in contrast to juvenile diabetics in whom there is no increase in liver fat

Arteriosclerotic lesions are extraordinarily prevalent in patients with diabetes This is discussed more fully in the section on *Complications*

Clinical Symptoms and Signs In children and young adults an abrupt onset or one which can be dated within a two months period is encountered in about 65 per cent of patients according to Joslin In the older age groups the onset is usually so insidious that it cannot be established Among these patients the disease is often discovered only in the course of routine examination of the urine because if symptoms do exist they are not sufficiently severe to cause the patient to seek medical attention Other patients more *than forty* years old first see the physician when a complication arises suggesting that diabetes may have been present but unrecognized for years

The most common and characteristic symptom of diabetes and the one from which it derives its name is *polyuria* Patients not infrequently pass large amounts of urine day and night and the volume is often in excess of 3 or 4 liters Inordinate thirst *polydipsia* may torment the patient and lead him to seek medical advice Less frequent but not uncommon is a striking increase in appetite *polyphagia* This is particularly true in children who are brought to the physician by parents because despite a great improvement in appetite the children fail to gain weight or strength Many patients complain of *loss of weight* or *loss of strength* or both losses of 20 to 40 pounds in the course of a few weeks or months being not unusual The symptoms of polyuria polydipsia polyphagia loss of weight and loss of strength are generally associated with the more acute and severe forms of the disease Among older patients there may be an abnormal tendency to postprandial *drowsiness* not related to ketosis at times there are vague aches in the legs or other symptoms as already mentioned referable to some complication

In uncomplicated diabetes there are but few *physical signs* which alone would lead one to suspect the disease Possibly marked emaciation and dryness of the skin and mucous membranes without obvious cause might be considered evidence In uncontrolled diabetes in children hepatomegaly is common and is at times associated with splenomegaly

The characteristic feature of the *urine* in diabetes is obviously the presence of glucose The concentration of sugar may vary from mere traces to as much as 10 per cent and the total excreted in twenty four hours varies from insignificant amounts to several *hundred grams In general* the amounts excreted are indicative of the intensity of the disorder at the time In the presence of ketosis the urine usually contains large quantities of ketone bodies which can be detected by the nitroprusside and ferric chloride reactions Proteinuria and numerous casts are often present in ketosis The *blood sugar* level may be normal or markedly elevated depending upon the circumstances of the test and the severity of the disease in severe uncontrolled diabetes it may exceed concentrations of 1000 mg *per 100 ml It has already* been mentioned that blood lipids are often increased in

diabetes particularly when ketosis is present When emaciation is marked hypoproteinemia may be extreme and there is a sharp reduction in the serum albumin fraction with some increase in alpha 2 globulins It is rare at the present time to find cases which have reached this stage of protein depletion In uncomplicated diabetes there is no reduction in the *erythrocyte count* except in the presence of marked malnutrition when mild secondary anemia may be present With severe dehydration in ketosis hemoconcentration may be moderate The *leukocyte count* is normal except in severe ketosis and acidosis when it usually rises to 20 000 or 30 000 per cu mm The *sedimentation rate* of the red cells is essentially normal except in the presence of acidosis or complications of infectious origin

Complications With the increasing span of life of patients with diabetes complications may be expected to increase consequently they deserve particular consideration in management of the disease

Acidosis and Coma In days before the advent of insulin approximately 50 per cent of diabetics died from these complications Today death in coma is a rare occurrence in well organized clinics and a case terminating fatally deserves critical review to determine the reasons for coma and for failure of therapy Whereas deaths from acidosis have become a rare occurrence it must be emphasized that any diabetic may succumb in two or three days if control of his disease is not rigidly exercised Ketosis with its sequelae acidosis and coma is usually precipitated by one of the following disorders (1) infections of the respiratory genitourinary or gastrointestinal tract or pyogenic infections (2) surgical procedures or trauma (3) gastrointestinal disturbances with reduction of food intake or vomiting *The commonest contributing factor to ketosis in these conditions is the ill advised reduction or omission of insulin by the patient because of a decrease in food intake In reality all these disturbances effect an increase in the insulin requirement!* It should be emphasized that in many instances emotional disturbances are the basis for increases in glycosuria ketonuria "digestive disturbances and the subconscious or conscious rationalization for the withdrawal of insulin

The development of acidosis is usually associated with *symptoms* of increasing weakness weariness dull headache and general malaise The onset may be abrupt or insidious Insatiable thirst soon becomes a prominent feature and as acidosis progresses hyperpnea or the air hunger' of Kussmaul appears with little if any subjective distress Epigastric aching pain adds to the discomfort of the patient and is associated with increasing nausea and vomiting and persistent thirst The abdominal symptoms in association with the striking leukocytosis usually present in severe ketosis often arouse suspicion of acute inflammation in the peritoneal cavity The patient becomes more and more listless and may sink into coma quietly and die or coma may be preceded by a period of great restlessness irritability and confusion

On *physical examination* the patient in severe diabetic acidosis shows marked dehydration of the mucous membranes and loss of turgor of the skin The eyes are sunken the lips and tongue red and parched and the cheeks either flushed or else very pale The breath has the characteristic fruity odor of acetone and hyperpnea is apparent These signs are accompanied by a rapid feeble pulse a temperature which may either be elevated or subnormal and by arterial hypotension The blood pressure may fall to 60 to 70 mm of mercury as coma deepens and anuria supervenes together with progression of peripheral circulatory collapse In older patients this state of shock if allowed to continue gives rise to myocardial insufficiency probably because of decreased blood flow in the coronary arteries

The *severity* of diabetic acidosis may be arbitrarily but conveniently classified in relation to the bicarbonate combining power of the blood serum When the serum carbon dioxide content falls below 25 volumes per 100 ml severe acidosis may be said to be present A carbon dioxide of 25 to 40 volumes per 100 ml may be considered indicative of moderately severe acidosis and values between 40 and 50 volumes are consistent with mild acidosis This is a purely clinical classification and is not correlated with actual shift of the *p*H from normal which is obviously more significant than is the CO level Deep coma due to ketosis and acidosis rarely if ever develops with a blood carbon dioxide above 25 vol umes per 100 ml When the carbon dioxide is higher it is particularly important to exclude other causes of coma The other typical blood and urine findings have been described It should be added for *emphasis* that loss of bicarbonate and also of chloride results from their replacement by

ketone acids and from a loss of sodium from the blood and intercellular fluids by renal excretion *In the presence of renal failure occurring in the course of peripheral circulatory collapse ketone bodies may virtually disappear from the urine Failure to appreciate this fact may result in failure to recognize severe diabetic acidosis* In these patients large quantities of acetone can be demonstrated in the blood plasma with the simple nitroprusside reaction Patients exhibiting renal insufficiency may also have retention of nonprotein nitrogen in excess of 200 mg per 100 ml

Kidneys With the lengthening of the life span of diabetics renal complications assume a progressively more frequent and serious role The commonest namely *pyelonephritis* may be wholly asymptomatic and recognized only by recurrent or constant mild proteinuria and pyuria It may however be associated with typical acute symptoms With progressive disease hypertension and uremia often supervene

The most characteristic renal complication of diabetes is *capillary glomerulosclerosis* in which hyaline globules appear in and between the capillary loops When the process is marked it is often associated with the Kimmelstiel Wilson nephrotic syndrome characterized by proteinuria hypoaluminemia with increase in alpha 2 globulin edema and arterial hypertension In the milder cases there may be only proteinuria with or without hypertension This disorder occurs infrequently in patients whose diabetes is of less than five years duration and appears to be frequent when diabetic control has been poor Its incidence varies with the criteria set by individual pathologists but is of the order of 20 per cent in many autopsy series The lesion is best diagnosed in life by *renal biopsy*—this is of particular importance in its differentiation from low grade pyelonephritis The management of the Kimmelstiel Wilson syndrome is that of chronic nephritis

Capillary glomerulosclerosis is often associated with diabetic retinopathy and neuropathy these together are known as the diabetic triopathy which some authorities believe to represent a different form of diabetes The evidence for this view is not convincing Of interest is the fact that as renal failure progresses usually slowly in capillary glomerulosclerosis insulin requirements decrease perhaps because of a decline in renal insulinase activity *Necrotizing papillitis* should be suspected in diabetics exhibiting renal shut down in association with severe acidosis particularly with circulatory collapse or in sepsis This disorder is encountered most frequently with diabetes but it occurs also without it

Arteriosclerosis Because about 50 per cent of diabetes occurs in the fifth and sixth decades it is to be expected that arteriosclerosis in its various forms will appear concurrently It seems however that the two disorders are more intimately related since 50 per cent of White s children who had diabetes for more than fifteen years had calcification of leg vessels How much metabolic factors such as long-continued hyperglycemia and hypercholesterolemia contribute to the arteriosclerotic process is not known It is of interest that Mendlowitz has demonstrated decreases in digital blood flow in young diabetics and that this change is largely independent of intensity and duration of the diabetes and the age of onset Lax and Feinberg have demonstrated in many diabetic children changes in the pulse wave characteristic of arteriosclerosis or hypertension Furthermore 11 of 21 children of diabetic parents showed these changes although they were not diabetic themselves at that time This suggests the possibility that the vascular lesions may be at least in part unrelated in their genesis to the intensity and duration of overt disturbances in carbohydrate metabolism Decrease in circulation in the legs gives rise to *trophic ulcers* in the soles of the feet and also serves as a basis for *infection* and for *gangrene* one of the most serious complications of diabetes It is generally believed that these complications appear most frequently in neglected *diabetes of long standing It seems possible* that neglect of the feet dermatophytosis and secondary infection in patients with compromised circulation are of greater importance Angina pectoris and *cardiac infarction are extremely common* in older diabetics This is of importance in relation to the management of older patients with insulin

Eyes Retinitis may occur in diabetics with or without hypertensive vascular disease and may appear as early as the second decade of life This disorder is ten times as frequent in patients who have had their disease for fifteen years as it is in patients in whom diabetes has been known only one year It is generally believed that the diabetic retinitis is most apt to develop in patients with poorly controlled diabetes or in those who have been given a diet high in fat and low in carbohydrate *The most characteristic* lesion is

aneurysmal dilatation of the finer blood vessels often simulating punctate hemorrhages Hemorrhages are also common and frequently occur in association with waxy and cotton wool exudates Later proliferating retinopathy and advanced arteriosclerosis are found

Cataracts may develop in young diabetics but their incidence is extremely low Senile cataract is common in older diabetic patients but perhaps no more so than in nondiabetic persons of the same age group

Nervous System Rundles has reported 125 cases of diabetic neuropathy among 3000 diabetics These include peripheral neuritis with motor and sensory changes most frequently involving the legs as well as lesions of spinal nerve roots and autonomic disturbances involving the bladder and vasomotor apparatus There are no clinical signs which with any regularity serve to distinguish diabetic neuritis from neuritis due to other causes with the exception of miserable pain which is a particularly prominent feature of diabetic neuritis Associated with the diabetic neuropathies there is often an increase in spinal fluid protein which may reach 200 mg per 100 ml

The basis for neurological lesions is not established It seems unlikely that vitamin B_1 or B_1 deficiency to which it has been ascribed plays any part Probably some of the diabetic neuropathies result from "ischemic neuritis due to sclerosis of the vasa nervorum In the opinion of Rundles the neuropathies are caused by other metabolic disturbances which appear in the course of poorly controlled diabetes In support of this view is the fact that striking improvement frequently follows a period of adequate regulation of the disease Probably multiple factors play a part in the genesis of the diabetic neuropathies Mirsky has reported that diabetics regardless of duration of their disease intensity or age at onset exhibit a diminution in vibratory sense equivalent to that in nondiabetics two decades older This suggests that neurological lesions like vascular lesions may not be correlated with the disturbances in carbohydrate metabolism Diabetic neuropathies are encountered from the first decade on In Rundles series however about 17 per cent appeared in the sixth decade alone

Diabetics are particularly susceptible to cerebral infections with *mucormycosis* The syndrome including uncontrolled diabetes mellitus associated with ophthalmoplegias signs of meningoencephalitis and often sinusitis should arouse suspicion of this infection which is usually but not invariably fatal

Skin Furuncles and carbuncles are sufficiently frequent in patients with diabetes to make examination of the urine for glucose mandatory in any person suffering from these pyogenic infections Pruritus of a generalized nature is an occasional complication of diabetes but pruritus is much more commonly limited to the vulva Pruritus vulvae is frequently associated with infection due to *Monilia albicans*

Numerous observers have commented on the presence of xanthochromia in diabetes Rabinowitch Ralli and others showed this to be the result of an increase in the circulating carotene which occurs because of an apparent decrease in the capacity of the liver of the diabetic to convert carotene into vitamin A Xanthochromia is not to be confused with xanthoma diabeticorum a relatively rare disorder characterized by nodules commonly on the elbows ulnar surfaces of the forearms and knees and usually associated with hypercholesterolemia

Tuberculosis The incidence of pulmonary tuberculosis is about four times higher among diabetics than among nondiabetics The two diseases occur together with sufficient frequency so that all diabetics should have roentgen ray study of the chest as part of their routine examination

Course and Prognosis At the present time diabetes mellitus must be looked upon as a chronic and incurable disease There is a tendency for it to progress in intensity with time but there are many exceptions to this generalization The fluctuations in intensity of the disease in any patient have already been commented upon Richardson found that in a group of 55 patients followed for more than five years the insulin requirement increased in 21 and actually decreased in 10 In a group of 45 patients who did not require insulin for regulation 21 were still able to remain sugar free without insulin after five years of observation

The average duration of life in diabetics in all age groups according to Joslin has increased from 4 9 years in pre insulin days to about 13 years at the present time The most striking increase in the anticipated span of life is in the young For example in an analysis of Joslin s material it appears that the life expectancy of a child of ten years with diabetes is forty years in contrast with the normal expectancy of fifty seven years At sixty the anticipated duration of life is ten years in contrast to the

normal of sixteen years (Metropolitan Life Insurance Company)

The actual cure of diabetes mellitus is probably a rare occurrence In the obese as mentioned under Etiology it is not unusual to find a reversion to normal carbohydrate metabolism with a return to a more normal weight In these persons diabetes should be considered "latent rather than cured because a return of obesity is associated with a return of overt diabetes In hyperthyroidism likewise relief of this disorder may cause mild diabetes to become latent With growths of the adrenal glands in which diabetes results from the elaboration of antiinsulin e g Cushings syndrome diabetes may be relieved by removal of an adrenal cortical tumor

Classification Patients are usually classified as having mild moderately severe or severe diabetes and yet the basis for such classification is wholly arbitrary and quantitatively ill defined There would be general agreement that a diabetic requiring only moderate restriction of his diet for adequate control of his disease could be termed as having mild diabetes Furthermore if in the absence of insulin therapy heavy glycosuria loss of weight and acidosis tend to develop all would agree that the disease is severe

The dosage of insulin required for the regulation of diabetes also serves at times as a general guide for classification However it has been indicated elsewhere that certain endocrine and other factors determine insulin requirements hence exceptions to the use of insulin dosage as the grounds for classification have to be made For example a girl with Addisons disease and diabetes who excreted 60 to 80 gm of glucose daily without insulin could scarcely be classified as having mild diabetes merely because in these circumstances her insulin requirement was only 4 to 6 units a day Adding still further to the difficulty of definite classification of diabetes is the fact that the individual patient may fluctuate from one category to another Thus mild diabetes may in the course of an acute infection become severe only to revert to a milder form with subsidence of infection

Diagnosis The diagnosis of diabetes mellitus affords no difficulty when polyuria polydipsia and polyphagia are associated with an elevation of the fasting blood sugar level and with glycosuria Even in the absence of symptoms glycosuria related to the ingestion of carbohydrate and a post absorptive blood sugar concentration in excess of 120 mg per 100 ml constitute an adequate basis for the diagnosis The presence of glycosuria is however not essential for the diagnosis because the renal threshold may be significantly elevated in certain older diabetics In this group the fasting blood sugar may be as high as 200 mg per 100 ml and glycosuria may appear only after meals if the blood sugar exceeds levels as high as 300 mg per 100 ml

Diabetes mellitus should be suspected in any person who exhibits glycosuria in relation to food intake on an unrestricted diet or whose venous blood sugar level rises above 170 mg per 100 ml at any time In these patients the form of the blood sugar curve following either a carbohydrate rich meal (containing potato three slices of bread a sugar containing dessert and sugar in coffee) or a glucose tolerance test may prove helpful in establishing the diagnosis of latent diabetes The *glucose tolerance test may be carried out by determining the* blood sugar level before and after the oral administration of 1 to 1 75 gm of glucose per kg of body weight in the fasting state The blood sugar should be determined before and one and two hours after the administration of glucose and urine collected at these times should be tested for sugar Normally the blood sugar does not rise above about 150 mg per 100 ml in one half to one hour after the ingestion of the glucose and returns to a normal level in two hours and the urine remains sugar free If higher levels are reached or *if the blood sugar does not return to normal in two hours diabetes should be suspected* Conn suggests that 11 oxysteroids given in *conjunction with glucose tolerance* tests unmask otherwise undetectable diabetes

Beaser has pointed out that cognizance should be taken of the presence of 'latent" diabetes characterized clinically only by a diabetic glucose tolerance curve and possibly transient glycosuria When these occur particularly in persons with a family history of diabetes the avoidance of obesity and the restriction of dietary sugar may prevent the establishment of overt diabetes

The *interpretation of the glucose tolerance test* is to a great extent dependent upon the conditions under which it is carried out The state of nutrition and the nature of the diet preceding the test are of prime importance This is graphically demonstrated in Figure 70 Thus the curve characteristic of diabetes occurs in patients with undernutrition or in those who have maintained a diet low in carbohydrates

whereas in the same person after the liberal ingestion of carbohydrate for a few days prior to the test normal responses are evoked As has been mentioned before this diabetic type of response following undernutrition *or the administration of insulin* to the normal is characteristic of "starvation diabetes Likewise as stated before this temporary decrease in glucose tolerance may in part result from "rest" of islet tissue with a decrease in the elaboration of insulin It is well established also that the effectiveness of insulin in man and animals is in general reduced by starvation or by low carbohydrate diets *and on the other hand it is increased by* the liberal ingestion of carbohydrate and by hyperglycemia It is therefore important to bear in mind that *glucose tolerance curves typical of diabetes may signify undernutrition or carbohydrate starvation and not necessarily the presence of diabetes mellitus*

Errors in the diagnosis of diabetes may occur from faulty appraisal of normal or low blood sugar values obtained after strenuous exercise If a person either normal or diabetic exercises after the ingestion of carbohydrate an appreciable reduction in blood sugar occurs in association with an increase in utilization of glucose

Transient hyperglycemia and glycosuria *occur in a good many circumstances and* may not signify the presence of diabetes mellitus For example as stated elsewhere transient hyperglycemia and glycosuria occur frequently in hyperthyroidism Hyperglycemia and glycosuria also occur after the injection of epinephrine and on the same basis during acute emotional strain or in the presence of certain tumors of the adrenal medulla A few nondiabetic persons have a brief rise in blood sugar above their renal thresholds and excrete traces of glucose after the ingestion of large amounts of sugar—this is known as *alimentary glycosuria* Hyperglycemia and glycosuria occur not infrequently in severe meningitis and in certain injuries to the brain The history and other findings serve to differentiate these disorders from diabetes mellitus

An unusual condition in which considable quantities of glucose appear in the urine is *"renal glycosuria"* In at least certain cases this results from an inborn error of metabolism in which the normal reabsorption of glucose fails to take place in the renal tubules (Fanconi s syndrome) Patients with this disorder resemble animals poisoned with phlorizin in that they do not have hyperglycemia and the degree of glycosuria is essentially independent of

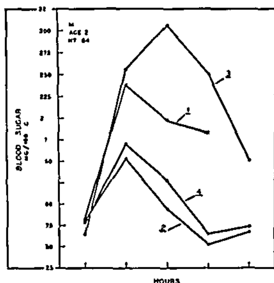


Fig 70 Effect of diet upon the glucose tolerance curves (after Conn) 1 Test done on admission in severe undernutrition 2 After two weeks 3000 cals 300 gm CHO 80 gm P 3 After seven days 1600 cals 20 gm CHO 50 gm P 4 After seven days 3000 cals 300 gm CHO 80 gm P

the carbohydrate intake Young people with alimentary glycosuria or renal glycosuria should be considered potential diabetics and should be reexamined at frequent intervals particularly when a family history of diabetes has been elicited

Lactosuria is not uncommon in pregnancy but is not related to diabetes mellitus Levulosuria galactosuria pentosuria and maltosuria are rare conditions not as a rule associated with elevation of the blood sugar The nature of the sugar excreted should be determined in all cases of atypical glycosuria

Treatment During the past decades the treatment of diabetes has become greatly simplified and it should now be the responsibility of the family physician rather than the specialist to treat the numerous patients who seek his aid Nevertheless it cannot be overemphasized that the successful treatment of diabetes continues to demand the closest attention to detail by both the *physician and the patient*

The aim of therapy in diabetes mellitus should be directed towards maintaining health happiness and normal nutrition on a regimen which keeps the patient approximately sugar free * This can be achieved

* The aim of maintaining the patient approximately sugar free has been challenged by Tolstoi who administers insulin and disregards the degree of glycosuria provided that ketonuria and the loss of nitrogen do not develop It remains for the future to determine whether *or not this seeming laxity in* management will add materially to the incidence of arterial disease neuropathies and retinitis

easily in the vast majority of patients with but little modification of the patient's way of life In a few patients the so called brittle diabetics satisfactory regulation is extraordinarily difficult even for the specialist to achieve and in these patients intermittent glycosuria is preferable to a life dedicated to the testing of urine

The management of diabetes must be based upon two principles The first is the establishment of a dietary *regimen* with or without insulin in accordance with the aims set forth for therapy The second is the education of the patient so that he understands (1) the nature of the fundamental disorders in his disease (2) the preparation and regulation of his diet (3) the method of testing his urine for sugar and ketone bodies (4) the technique of self administation of insulin when this is required and (5) the complications which may occur and how they should be met The diabetic patient should be taught to assume the role of the physician and the latter should assume the role of the consultant in routine management of this disease These principles are put into practice most simply and effectively and with the least loss of time if the patient with severe disease is hospitalized for regulation and training at the time the diagnosis is established At the outset the importance of the patient's reactions to his life situations cannot be overemphasized in terms of the success or failure of therapy

One of the first and most important questions which arise in the regulation of a diabetic is whether insulin will be required or whether dietary restriction alone will suffice to achieve the aims of therapy Upon the decision reached will depend the *amount and distribution of the carbohy*drate in the diet frequency of collection of urine specimens the times of meals the economic factor involved in the provision of insulin and to a large extent the education of the patient Whether or not insulin will be required cannot be answered dogmatically and the method of trial and error must frequently be invoked This is particularly true in patients whose disease process for one reason or another may at one time be severe and at another time mild For example in the presence of infection or hyperthyroidism insulin therapy may be essential and yet after subsidence of activity dietary regulation alone may suffice In spite of these apparent difficulties in arriving at an important decision the following generalizations can be made and serve as useful guides (1) the majority of older obese patients in whom the disease is essentially without symptoms do not require insulin and (2) all diabetic *children young adults and most older* patients who acquire the disease acutely with the characteristic symptoms of polydipsia polyuria rapid loss of weight and strength require insulin therapy The percentage of patients with diabetes who can be regulated *without insulin varies in different clinics* according to the type of regimen established the standards for adequate treatment the intelligence of the patients as a group and many other factors Accordin to Adlersberg and Dolger 46 per cent of *their series of 1131 patients more than four*teen years of age did not require insulin and were treated with diet alone These patients were undoubtedly in the older age group and were presumably overweight

Dietary Treatment without Insulin This form of treatment as mentioned before is applicable only to the management of the relatively mild diabetes encountered in obese patients most of whom are more than fifty years of age As stated under Etiology the control of obesity in these patients usually suffices to render the urine sugar free and to reestablish an essentially normal blood sugar level It is rarely necessary nor is it advisable to attempt to reduce body weight all the way to the ideal value in these patients Furthermore reduction in weight should be gradual since rapid reduction with extreme curtailment of carbohydrate may initiate ketosis and intensify the diabetic process If regulation is not accomplished without the establishment of undernutrition or if loss of weight is accompanied by significant *loss of strength or marked ketosis* insulin therapy is indicated

The most important rigid dietary restriction to be initiated is the *omission of free sugar from the diet* This includes candy cake ice cream made with sugar pastry fruits preserved with sugar jam and so on When sweetening is desired saccharin should be used in the preparation of foods The diet should be limited as to its content of foods containing high concentrations of starch *e g* bread potato macaroni spaghetti rice cornstarch or tapioca The pa*tient should not be allowed more than* three slices of bread daily and and more than one small serving of any of these other foods mentioned The reason for these limitations is the fact that the availability of glucose in foods having high concentrations

of carbohydrates results in rates of absorption which may exceed the rate of utilization by the diabetic and therefore may give rise to hyperglycemia and glycosuria The remaining carbohydrate of the diet should be in the form of vegetables and fruit with relatively low concentrations of carbohydrate *e g* 12 per cent or less It is desirable to have the daily carbohydrate ration divided approximately equally in the three meals

Protein should be permitted as desired but for most patients 1 to 1 5 mg per kg of "ideal" weight is sufficient Fats may be allowed in any form but the total daily food intake should not exceed 1200 to 1500 calories Care must be taken in the selection of foods in this limited regimen to provide for vitamin requirements

When the desired reduction in body weight has taken place and the urine remains sugar free the caloric intake may be gradually increased to prevent further weight loss If this increase in diet results in the reappearance of glycosuria or of a fasting or two-hour postprandial blood sugar level in excess of perhaps 150 mg per 100 ml treatment with insulin becomes indicated

Patients following this simple type of regimen should during the period of desugarization collect twenty four hour specimens of urine to be tested for sugar and ketone bodies After the urine becomes sugar free the patient should test an early morning specimen for glucose—this should then become a lifetime habit

There is no need for frequent determinations of the blood sugar level in these patients When the urine becomes sugar free it is well to determine the fasting level in order to establish whether or not an unusually high threshold is present Thereafter it may be of interest to determine the fasting blood sugar level at intervals of about six months unless complications intervene

Treatment with Insulin When the decision to use insulin has been reached time is saved if the patient is at once started on the *diet* which it is anticipated will meet his energy requirements and as far as possible his desires The *amount of carbohydrate* which the diet should contain has long been a matter of controversy In the opinion of the writer the satisfaction of the patient and his nutritional state are the important determining factors Most patients are satisfied with diets containing 150 to 250 gm of carbohydrate Insulin treated patients as well as those being treated with diet alone should not be permitted the use of free sugar

The *distribution of carbohydrate* among the three repasts is a matter of detail which however assumes great importance in successful regulation The optimal distribution depends upon individual responses and still more upon the type of insulin used There is therefore no hard and fast rule to be followed in the partition of the daily carbohydrate ration but when the slow acting protamine zinc insulin (PZI) is used the majority of patients are best controlled when the carbohydrate ration is divided into 1/ , and among breakfast lunch and dinner or when part of the evening ration (*e g* a slice or two of bread and butter) is saved for a bedtime feeding When globin NPH or lente (IZS) insulin is employed more frequently part of the noon ration is needed in mid afternoon to avoid shock If the carbohydrate of a patient receiving protamine zinc insulin is divided into thirds it may be expected that the patient will experience hypoglycemia in the early morning hours and heavy glycosuria after breakfast This phenomenon may be termed *paradoxical glycosuria* since the hyperglycemia and glycosuria probably result from epinephrine release following intense hypoglycemia during sleep It can be established by determining the blood sugar level at about 3 A M and should be treated by reducing the dosage of long acting insulin If a patient has been established on a regimen with regular insulin given twice daily (a regimen rarely indicated today) distribution of the carbohydrate ration into 1/ and usually proves the most satisfactory When a mixture of regular insulin and protamine zinc insulin or NPH insulin is used or when globin insulin or lente insulin is given many patients are best controlled with carbohydrate divided equally among the three meals However individual variations are great and many patients require a part of the noon ration of carbohydrate in mid afternoon and others require part of the dinner ration at bedtime for satisfactory control as with PZI The important point to be borne in mind is that *the distribution of the carbohydrate among the three meals without any change in insulin dosage often determines the success or failure of therapy*

The amount of *protein* in the diet should be determined by the amount necessary for normal nutrition and by the patient s desires In most cases amounts between 60 and 100 gm daily prove adequate to meet these demands

When the carbohydrate and protein rations have been decided upon enough *fat* should be included to provide the calories necessary to fulfill energy requirements If patients exhibit a distaste or intolerance for fat or if their desires for carbohydrate are not satisfied the latter foodstuff should be increased and the fat correspondingly decreased Rigid control of the fat intake is of considerably less importance for satisfactory regulation as might be expected than is control of the total carbohydrate intake and its distribution in the meals How much the rigid restriction of fat and cholesterol will decrease the diathesis for atherosclerosis in diabetics remains to be established

During the period of regulation in the hospital it is most helpful to have the patient deviate as little as possible from his anticipated way of living both with regard to physical activity and time of meals otherwise many unnecessary adjustments of diet and insulin become essential when the patient returns to his home and normal existence

In the education of the diabetic regulated with insulin it is essential that he be instructed promptly in the preparation of a standard diet from which in the future he will be able to make indicated adjustments and add to the variety of his meals with the aid of tables of food values (The *Diabetes Guide Book* of the American Diabetic Association will be found most helpful to physicians and patients in the preparation of menus)

During the regulation of patients treated with insulin the *urine* should be collected in four parts during each twenty four hours the first sample from before breakfast up to lunch time the second from before lunch to before dinner the third from before dinner to bedtime and the fourth from bedtime to the next morning Adjustments in insulin dosage the type of insulin used and distribution of carbohydrate depend to a large extent upon a knowledge of the time of day at which heavy glycosuria tends to persist Quantitative determinations of the sugar in the urine are not deemed essential for regulation of the patient

The *type of insulin to be used in treatment* is to a great extent a matter of choice but the majority of patients can be treated successfully and with the least inconvenience with a single dose of NPH globin or lente insulin About 75 per cent require 40 units or less about 10 per cent require 65 to 80 units With the advent of long acting insulin preparations and particularly with mixtures such as NPH the former bugbear of two or three injections daily for routine management has been obviated in almost all cases In patients requiring 40 units of insulin or less a single injection of NPH is usually equivalent to the same dose of PZI and the fluctuations of blood sugar are less wide Also night hypoglycemic reactions are less frequent These comments apply to the use of globin and lente insulin preparations also Today in many clinics insulin zinc suspensions (IZS) are considered the insulin of choice for satisfactory regulation and to avoid sensitization reactions

In apparently mild cases treatment may be initiated with a dose of 10 to 20 units of long acting insulin given subcutaneously one half hour before breakfast if the diabetes appears severe it may be necessary to start with 40 units When heavy glycosuria is present time may be saved if supplementary doses of regular insulin are used in the first few days of regulation For convenience each voiding should be tested for sugar with Benedict s reagent If a red or orange precipitate forms 10 units may be given and if a yellow or green color appears 5 units should be administered Further decisions concerning the type of insulin its dosage and the distribution of carbohydrate depend on the response of the individual patient During regulation changes in insulin dosage should when possible be made not more frequently than every other day since time is obviously required for physiological adjustment to each change Except in the presence of heavy glycosuria acidosis or recurrent hypoglycemia changes in daily dosage in excess of 5 to 10 units should be avoided

The intensity and persistence of glycosuria in patients with essentially normal renal thresholds are more important criteria for therapy than are blood sugar levels which may show wide diurnal fluctuations and may at any moment bear little relation to the over all control of the disease In elderly diabetics with unusually high thresholds blood glucose determinations are obviously of importance In these arteriosclerotic patients some degree of hyperglycemia is preferable to hypoglycemia which often precipitates coronary insufficiency

In rare instances patients acquire extraordinary *resistance to insulin* and may be given in excess of 2000 units in a day without significant effect on the blood sugar level or on glycosuria Lowell found

that one patient acquired a neutralizing antibody for insulin which disappeared after the withdrawal of insulin and reappeared some time after insulin treatment was reinstituted Local or generalized urticarial reactions constitute the most common allergic response to insulin This reaction may vanish spontaneously or it may be controlled by antihistaminic drugs or by the use of lente insulin preparations not containing protamine The combined use of 11-oxysteroids and crystalline insulin may be of value in the management of extreme insulin resistance

Hypoglycemic reactions are likely to occur from time to time in any patient treated with insulin In most instances reactions are mild transient and easily controlled Occasionally particularly in patients receiving large doses of long acting insulin protracted or fatal reactions occur and are associated with punctate hemorrhages and other changes characteristic of cerebral anoxia With intense and prolonged hypoglycemia there may be an increase in the number of cells in the spinal fluid and changes in the electroencephalogram may persist for days or weeks

The *symptoms of hypoglycemia* commonly known as "*insulin shock*" do not make their appearance at any definite level of blood sugar but the diagnosis should be considered doubtful if the blood sugar is over 60 mg (Folin Wu method) or perhaps 45 mg (Somogyi Nelson method) per 100 ml In some patients the symptoms of insulin shock do not appear until the blood sugar falls to 40 mg per 100 ml or even lower The symptomatology is extremely variable but each person tends to follow a reproducible pattern The commonest complaints in mild shock are a "trembly feeling inside an empty feeling in the epigastrium profuse sweating pallor rapid pulse and weakness which develop in the course of fifteen to thirty minutes These symptoms reflect the release of epinephrine and usually follow an abrupt fall in blood glucose In some cases unfortunately there may be none of these prodromal symptoms the attack may begin abruptly with disorientation confusion delusions aphasia ataxia even loss of consciousness or generalized convulsions A positive Babinski reaction and other focal neurological signs may be present In patients using long acting insulin the onset with symptoms of headache nausea and vomiting are common and tend to be insidious in their appearance and progression It is important to bear in mind that *shock following long acting insulin not infrequently appears as long as twenty four to forty eight hours after the last dose—particularly when large doses are given*

The administration of sugar constitutes the *treatment of insulin shock* Every insulin treated patient should carry a lump of sugar to be taken if suggestive symptoms arise This treatment or better a small glass of orange juice usually suffices to relieve mild symptoms in a few minutes If the patient cannot be prevailed upon to swallow 20 to 40 ml of 50 per cent glucose may be given intravenously When severe shock appears in patients taking large doses of insulin shock is apt to recur and is often resistant to treatment particularly if convulsions or loss of consciousness has persisted for some time In these cases a 1000 ml clysis of 5 per cent glucose may be needed to prevent the reappearance of hypoglycemia As an emergency measure 0 5 to 1 ml of *epinephrine* may be given subcutaneously to raise the blood sugar temporarily

Every diabetic treated with insulin should at all times be provided with an identification card stating that he has diabetes and takes insulin This is absolutely essential for patients have been killed when on admission to a hospital in hypoglycemic coma the presence of sugar in the urine has led to the administration of more insulin before the blood sugar has been determined There should be no confusion between the recognition of hypoglycemic coma and coma due to acidosis but a safe rule to be followed is to *administer glucose when in doubt* after a sample of blood has been taken for determination of sugar and carbon dioxide

Oral Chemotherapy A variety of chemical compounds have the capacity to lower the blood sugar of normal man and animals and that of some diabetics These agents include derivatives of sulfonylureas sulfonamides biguanides and other compounds

Most of these agents lower the blood sugar by injuring the capacity of the liver to elaborate or release glucose into the blood and have been discarded as highly toxic One compound 1 butyl 3 p tolylsulphonylurea *tolbutamide* is receiving wide spread clinical trial Surely many more chemical agents will be tried because of the laudable aim of finding an orally administered effective nontoxic substance to replace insulin therapy The mechanism of action of tolbutamide has not been clari

fied but evidence that it increases the utilization of glucose at the periphery is not compelling Yet its effect seems to be related to insulin activity as in most species it does not depress the blood sugar in the absence of the pancreas and it is essentially ineffective in juvenile (insulin deficient) diabetics It probably also inhibits hepatic glycogenolysis in high dosage

Tolbutamide lowers the blood sugar in about 65 per cent of all diabetics and about 80 per cent of older diabetics show a response It is *contraindicated* in juvenile diabetics and brittle older diabetics It also has no place in the management of diabetic acidosis It is most effective in mild obese elderly patients (insulin resistant) and probably a number of those treated have in reality had no need of insulin therapy *The drug does not reduce the need for meticulous control of diet* Patients are usually given initially 3 0 gm daily for two to eight days before breakfast and insulin dosage is slowly reduced Tolbutamide dosage is gradually decreased to maintenance levels of 1 to 2 gm daily

It must again be emphasized that tolbutamide does not appear to increase glucose utilization and is potentially dangerous About 3 per cent of patients exhibit side effects including urticaria and other skin rashes fever and some depression of bone marrow Alarming diabetic acidosis may develop in severe diabetics when tolbutamide treatment replaces insulin

Treatment of Acidosis When *severe* diabetic acidosis develops immediate and intensive treatment is indicated since recovery is the more likely the shorter the duration of symptoms The best treatment requires the coordinated effort of medical nursing and laboratory groups in a hospital

The treatment of diabetic acidosis must be directed primarily toward (1) *the restoration of salt and water* to the depleted circulating blood volume and interstitial spaces in order to arrest the progression of dehydration circulatory collapse and renal failure which lead to death and (2) *the correction of glycosuria ketosis and acidosis* which for reasons discussed elsewhere give rise to the loss of inorganic base and water

Upon admission the precipitating cause for the development of acidosis should if possible be promptly determined from the history and physical examination If an obvious infection *e g* pneumonia is present its treatment may be initiated simultaneously with that of the acidosis At the time of admission blood should be obtained for the *immediate* determination of carbon dioxide or pH sugar and urea and for grouping Through the same needle left in place an infusion of 1500 ml of physiological sodium chloride solution should be started and completed in one hour except in the presence of overt cardiac insufficiency when it should be given more slowly and preferably with measurements of venous pressure The patient should be given an initial dose of 100 units of regular or crystalline insulin subcutaneously If the blood pressure is below 90 mm of mercury half of this dose should be given intravenously If the blood glucose is in excess of about 700 mg per 100 ml an additional 100 units should be given at once *Long acting insulin should not be used in treating severe acidosis* If gastric dilatation is present or acidosis is accompanied by recurrent vomiting gastric lavage should be carried out with caution Fluids orally should be withheld until nausea has disappeared If the carbon dioxide is reported as less than 20 volumes per 100 ml (9 millimols per liter) a single dose *of 20 gm of sodium bicarbonate in* 1000 ml of water may be given intravenously Despite objection by some this *limited use of bicarbonate* has distinct advantages First it replaces directly and promptly one salt lost from the body *i e* sodium bicarbonate second it shortens the period of severe acidosis which is particularly deleterious to all patients in shock and third the utilization of carbohydrate is *decreased* by acidosis If the blood pressure does not rise or if severe peripheral circulatory collapse and oliguria are present the initial infusion should be followed at once by the administration of 500 ml of whole blood or an intravenous drip of norepinephrine

After the initiation of therapy as outlined insulin should be given hourly until ketosis has disappeared in most cases 50 units an hour prove adequate Stetten reports the presence of an insulin inhibitor in the alpha 2 plasma globulins in patients with insulin resistant ketosis *Urine specimens* should be obtained hourly by catheterization if necessary for sugar and ketone tests *Blood sugar and carbon dioxide determinations* should be made at least every 3 hours and if possible also a *serum* potassium determination It is advantageous to give enough glucose intravenously to maintain the blood sugar at about 300 mg per 100 ml as long as ketosis persists in order to increase the utilization of glucose and to avoid the possibility of superimposing hypoglycemic shock upon coma due to

ketosis and acidosis Frequently an infusion of 1000 ml of 5 per cent glucose in water given about three hours after the initial infusion is necessary to make adequate amounts of glucose available and to rehydrate the patient This solution also decreases the possibility of developing metabolic acidosis due to excessive concentration of the chloride ion and further dehydration resulting from osmotic diuresis due to the excessive sodium ion given Solutions of fructose have no practical advantage over those of glucose A number of workers suggest the use of complex hypotonic solutions of sodium chloride lactate and phosphate which may also include magnesium and potassium salts as well as some glucose Whereas there may in some instances be theoretical reasons for their use the mortality rates are not appreciably lowered by their employment Probably all patients with severe diabetic acidosis have a fluid deficit in excess of 5 liters which should be replaced parenterally or orally in twenty four hours

Occasionally significant *hypopotassemia* develops in the course of treatment of diabetic acidosis and results from continued loss of potassium in the urine and a shift of this ion to cells Decrease in serum potassium may be accompanied by profound muscle weakness involving the extremities and at times the diaphragm resulting in dyspnea Restlessness sweating and electrocardiographic changes may also be present In rare instances patients die from cardiac arrest This syndrome which rarely appears until after three or more hours of treatment with glucose and insulin is alleviated or can be avoided by the administration of 2 gm of potassium chloride given three or four times at hourly intervals by mouth If oral medication is not feasible 200 ml of 1 per cent solution of potassium chloride may be given *slowly* intravenously Preferable is an infusion of 1 liter of a solution containing 100 milliequivalents of sodium chloride and 40 milliequivalents of potassium chloride *Potassium salts should not be administered in the presence of oliguria or earlier than three hours after the initiation of treatment of the acidosis* because of possible potassium poisoning The fact that Joslin has successfully treated 90 consecutive patients suffering from severe acidosis without potassium salts indicates that the importance of hypokalemia is not great numerically When nausea has disappeared and ketosis is greatly lessened the patient may be given fluids by mouth on schedule Water broth gruel diluted milk or orange juice may be given in small amounts at a rate not exceeding 200 ml an hour Insulin at this time should be given in accordance with the degree of glycosuria the urine being tested every two hours If a red or orange precipitate appears 20 units should be given and if yellow or green 5 to 10 units should be administered A soft diet with a minimum of fat should be given for twenty four to forty-eight hours after ketonuria disappears and insulin should be administered in relation to the degree of glycosuria as just stated The patient may then be regulated on his usual diet

The outline of therapy of *severe acidosis* proves satisfactory in the majority of patients but many factors modify responses consequently deviations from this regimen must often be made For example *wide variations in the amount of insulin required are encountered in different patients* In the presence of persistent infection or hyperthyroidism several hundred units of insulin may be necessary and the tendency for ketosis to recur is great On the other hand the writer had a patient thirteen years of age who was admitted to the hospital in coma with a carbon dioxide of 15 volumes per 100 ml who became completely free of ketone bodies and sugar free with a total of only 85 units In the majority of cases 300 to 400 units are employed In older persons cardiac failure and pulmonary edema are apt to develop with the liberal administration of fluid given intravenously In these patients frequent examination of the chest for the appearance of basal rales and measurements of venous pressure serve as a useful guide Digitalization may prove helpful in this group If urinary suppression develops it should be treated as indicated elsewhere in this volume

In the presence of *mild or moderate acidosis* as defined elsewhere the patient should be put to bed the fluid intake should be increased to about 3 liters a day and sodium chloride to about 10 gm a day should be taken in the form of broth and enteric-coated tablets Carbohydrate in the form of fruit juices toast cereal potato rice and milk should be given up to 200 gm a day and fat should be reduced as much as possible in the diet The urine should be examined every two hours and regular insulin given at the rate of 20 units for a red or orange reaction and 10 for a yellow or green reaction The basis for acidosis must obviously be sought and corrected if possible

Treatment of Surgical Complications

Surgical procedures no longer constitute a great hazard to the patient with diabetes provided that rigid supervision is exercised It must be borne in mind however that surgical procedures and anesthesia are potentially capable of inducing ketosis Immediately before operation an infusion of 1500 ml of 5 per cent glucose in saline should be given and the patient should receive 25 units of regular insulin subcutaneously Another infusion and the same dose of insulin should be repeated after operation The urine should be tested for sugar and ketones at two hour intervals Regular insulin and not long acting insulin should be given as outlined in the treatment of mild acidosis Unless there are specific contradictions a light soft diet may be instituted on the second day and when the surgical condition permits the patient should again be regulated on his normal diet If an acute surgical condition *e g* appendicitis has been responsible for the development of severe acidosis operation should be postponed and antibiotics administered until after peripheral circulatory collapse has been treated

The treatment of *infections of the feet has benefited greatly from the* introduction of sulfonamide and penicillin therapy Even in the presence of a seriously compromised circulation there has been a striking decrease in the necessity for amputation

Retinitis Neuropathies and Arteriosclerosis The most important measure in the management of these complications is that of possible prevention by adequate dietary control of the disease Total ablation of the pituitary or the adrenal glands has been recommended to prevent the progression of diabetic *retinopathy At present these* procedures do not appear justifiable

Pregnancy in Diabetes The recognition and rigid control of diabetes in pregnancy is of paramount importance for maternal well being and the normal development of the fetus All pregnant women should have a two hour postprandial blood sugar determination in the third trimester Latent diabetes must be rigorously controlled The value of progesterone and estrogens in the pregnant diabetic is doubtful

Hygiene of the Diabetic A great decrease in the death rate from diabetes can be brought about by early diagnosis of the disease by frequent routine health examinations and by prevention of complications *through* education of the patient and cooperation of the physician

The patient should not be made unnecessarily introspective in the process of his education but he should never forget that he is a diabetic for laxness in attention to diet or to urine examination sooner or later results in serious consequences Exercise in moderation is to be advocated for *it actually increases carbohydrate utilization* to a certain extent Overfatigue both physical or mental worry unhappiness and lack of "peace of mind" decrease carbohydrate tolerance Any simple cold or other infection when it develops requires bed care the liberal ingestion of fluid and the immediate attention of the physician A patient should never for any reason lower his insulin dosage without first consulting his physician Likewise digestive "upsets require the advice of a physician Many cases of gangrene can be prevented in arteriosclerotic diabetics if they will care for their feet as well as they do their hands

Prevention Probably the most important factor in the prevention of diabetes mellitus *is the prevention of obesity in the community* in general In people with a family history of diabetes the avoidance of excessive weight is mandatory Experience dictates that "casual" or "alimentary" and "emotional" glycosuria are often forerunners of *overt diabetes and should be con*sidered as such Patients exhibiting these abnormalities should have two hour postprandial blood sugar determinations and should restrict the use of free sugar

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Spontaneous Hypoglycemia

Definition This term denotes a depression of the blood sugar to abnormally low levels usually in association with a characteristic group of symptoms which occurs without the administration of exogenous insulin

Etiology Seale Harris first recognized spontaneous hypoglycemia by symptoms resembling those which resulted from an excessive dose of insulin In 1924 he wrote "When I saw the insulin reaction in diabetic patients I realized I had seen many patients (not taking insulin) who had complained of the same symptoms *i e* hunger weakness and the anxiety neuroses" On the basis of symptomatology correlated with blood sugar determination Harris established the presence of spontaneous hypoglycemia in a number of patients The following classification (modified after Conn) indicates the wide variety of disorders in which spontaneous hypoglycemia may be encountered

- I Hypoglycemia associated with anatomical lesions—"organic"
  - A Hyperinsulinism
    - 1 Pancreatic islet-cell adenoma
    - 2 Pancreatic islet-cell carcinoma
    - 3 Diffuse hypertrophy or hyperplasia of pancreatic islet tissue
  - B Hepatic disease
    - 1 Toxic hepatitis
    - 2 "Fatty liver"
    - 3 Diffuse carcinomatosis
    - 4 von Gierke s disease (glycogen disease)
    - 5 Diffuse intrahepatic cholangitis
  - C Hypopituitarism (anterior lobe deficiency)—Simmonds disease
    - 1 Destructive lesions *e g* chromophobe adenoma and Rathke s pouch cyst
    - 2 Atrophy or infection
  - D Adrenal cortical insufficiency—Addison s disease
    - 1 Destructive granuloma—usually tuberculous
    - 2 Primary atrophy
    - 3 Destructive neoplasms
    - 4 Amyloid disease
  - E Hypothyroidism
  - F Lesions of the central nervous system *e g* thalamic
  - G Sarcomas and other tumors—mechanism unknown
  - H Alimentary functional hyperinsulinism—following gastric resection
- II Hypoglycemia without demonstrable anatomical lesions—"functional"
  - 1 Increased secretion of insulin by normal islet cells—autonomic imbalance?
  - 2 Decreased secretion of anterior pituitary or adrenal cortical hormones
  - 3 Excessive oxidation of carbohydrate in severe muscular work
  - 4 Pregnancy and lactation
  - 5 Idiopathic hypoglycemia of infants
  - 6 Malabsorption syndrome
- III Factitious hypoglycemia (surreptitious insulin administration)

The mechanisms producing spontaneous hypoglycemia in patients with pancreatic islet-cell tumors with destruction of the anterior lobe of the pituitary gland or with loss of adrenal cortical or thyroid tissue have a recognizable physiological basis Since hepatectomy is followed promptly by intense hypoglycemia it might also be expected that patients with diffuse disease of the liver would have spontaneous hypoglycemia regularly It is of interest however that whereas disorders of the liver contributes significantly to the total number of cases of spontaneous hypoglycemia reported its incidence in cirrhosis infectious hepatitis and ascending cholangitis is surprisingly low Hypoglycemia occurs in all cases of von Gierke s disease In a few instances hypoglycemia has been reported associated with lesions in the thalamus

In the majority of patients with spontaneous *hypoglycemia without demonstrable anatomical lesions* *i e* in cases of "functional" hypoglycemia there continues to be speculation concerning etiology It seems possible that an increase in secretion of insulin by the islet cells of the pancreas or a decrease in secretion of "anti insulin" by the pituitary or adrenal glands or the pancreas may be of importance but these changes if they do exist have not been demonstrated It is conceivable but not established that primary disturbances in liver function alter the utilization of carbohydrate without the striking demonstrable changes which for example occur in von Gierke s disease Hypoglycemia in pregnancy and lactation is possibly related to functional disturbances in the liver or in the endocrine glands which exert an effect on carbohydrate metabolism Whatever may be the etiology of "functional" spontaneous hypoglycemia its existence and importance cannot be doubted The relative frequency of various causes for spontaneous hypoglycemia has been analyzed and according to Conn 80 per cent of all cases result from one of three causes namely "functional" hypoglycemia hyperinsulinism with a demonstrable pancreatic lesion or organic disease of the liver

Morbid Anatomy It is clear from the classification of spontaneous hypoglycemia that a variety of pathological lesions may be encountered Whipple analyzed neoplasms of the islands of Langerhans present in a group of 149 cases of *hyperinsulinism* In this group 106 were benign adenomas 15 were outspoken carcinomas and the remaining 28 were questionably malignant Islet tumors occur most frequently in the body or tail of the pancreas and are often multiple but many escaping detection on surgical exploration are ultimately found to lie on the posterior surface of the head Multiple adenomas of the beta cells associated with hypoglycemia and with

functioning adenomas of the pituitary and parathyroid glands (*endocrine adenomatosis*) have been reported by Wermer Few cases of hypertrophy of the islands of Langerhans have been well documented The anatomical lesions of the liver the anterior lobe of the pituitary gland adrenal and thyroid glands responsible for the development of spontaneous hypoglycemia have already been mentioned

Long continued and intense hypoglycemia regardless of the cause gives rise to hemorrhages cerebral edema and other lesions in the brain that are characteristic of severe cerebral anoxia

Physiology The concentration of glucose in the blood is the resultant of physiological and biochemical forces engaged simultaneously in the transfer of glucose to and from the blood stream The body is normally protected against the development of hypoglycemia by various mechanisms discussed in the material on the physiology of diabetes mellitus A number of physiological factors are probably responsible for the wide range of clinical manifestations of hypoglycemia These may include (1) the liberation of epinephrine (2) a sharp decrease in cerebral O A V difference and an even greater fall in oxygen consumption by the brain without change in cerebral blood flow (3) the rate of decline of blood sugar (4) hypokalemia in certain instances and (5) variations in threshold for symptoms inherent in different persons

Alimentary functional hyperinsulinism occurring in patients after gastrectomy may result from excessively rapid absorption of glucose with hyperglycemia which stimulates excessive insulin secretion resulting in hypoglycemia

In severe liver disease hypoglycemia may ensue from the depletion of glycogen stores It may also result from the fact that the anti insulin effects of anterior pituitary extract and adrenal cortical steroids and glucagon on carbohydrate metabolism are probably to a considerable extent dependent upon normal liver function It is conceivable that there might be an increase in utilization of carbohydrate by the tissues in severe liver disease as a result of a decrease in the degradation of fat which takes place chiefly in the liver Finally it is possible that degradation of insulin is diminished in severe liver disease

In the course of severe physical exertion glucose utilization is increased perhaps because of increased penetration of glucose into cells and may result in transient hypoglycemia A decrease in blood sugar occurs in the diabetic as well as in the normal in exercise and therefore may result from an increase in carbohydrate utilization by tissue cells independent of the elaboration of insulin by the pancreas

Clinical Picture The pattern of the clinical picture in hypoglycemia is extremely varied but in a given person the same symptoms tend to recur though they vary in severity at different times The hypoglycemic syndrome is almost always episodic The attacks usually occur before breakfast or several hours after any repast and are frequently precipitated by physical exertion The episodes vary greatly in duration and intensity They may last but a few minutes and terminate either spontaneously or after the ingestion of food On the other hand they may be severe and last for hours or even days and prove resistant to treatment Occasionally an attack ends fatally The blood sugar level at which symptoms appear varies some patients are devoid of symptoms until levels below 40 mg per 100 ml are reached and others present classic symptoms with blood sugar concentrations of 50 mg per 100 ml The rate of fall of the blood sugar as well as the actual level reached may be a factor in determining the intensity and pattern of symptoms The symptoms usually associated with a rapid fall in blood sugar level probably result from sudden release of epinephrine and include sensations of hunger trembling inside pallor sweating tachycardia and weakness Symptoms arising from a more gradual and prolonged fall in blood sugar probably resulting from cerebral anoxia include headache visual disturbances disturbances in deep reflexes apprehension confusion delusions of grandeur focal or generalized seizures and coma The electroencephalogram often shows focal or widespread dysrhythmia which is usually transient but may persist for days or even weeks with or without focal signs after a prolonged and intense bout of hypoglycemia

Diagnosis To establish the diagnosis of spontaneous hypoglycemia it is essential to demonstrate a depression of the blood sugar level below 55 mg per 100 ml (Folin Wu method) or 45 mg per 100 ml (Smogyi Nelson method) In view of the fact that the periods of hypoglycemia are often transient various means must at times be used for their detection Four procedures may be recommended (1) Of foremost importance is the determination of the blood sugar level before breakfast although it may be normal in many cases (2) A blood

sugar determination should be made if possible at the onset of an attack If the attack is convulsive in nature the blood sugar toward the termination of the episode may be normal or even elevated (3) The glucose tolerance test has limited value and is of use only in patients in whom the fasting blood sugar is normal or in whom it has been impossible to procure a sample at the beginning of an attack The test is most valuable in the recognition of patients with *functional hyperinsulinism* who always exhibit a normal fasting glucose level but who develop hypoglycemia with levels below 55 mg per 100 ml (Folin Wu) in response to a stimulating dose of glucose Hypoglycemia is maximal between three and five hours after the ingestion of glucose (4) When hypoglycemia is not demonstrable by these means a twenty four to forty eight hour fast should be instituted and blood sugar determinations should be made at six hour intervals Patients with *insulin secreting tumors* usually exhibit progressive hypoglycemia with a continuing fast The prompt alleviation of symptoms and also modification of the electroencephalographic pattern in the direction of the normal with the administration of glucose affords strong evidence for the diagnosis of spontaneous hypoglycemia

The chief problem of diagnosis from the standpoint of management of the patient is to differentiate if possible *hyperinsulinism* due to organic disease of the islands of Langerhans from *functional* hypoglycemia Both these disorders often escape recognition for months or even years As a general rule the attacks in functional hypoglycemia are recognized by the response of the blood sugar to glucose stimulation" Furthermore functional" hypoglycemia is apt to occur in association with one of the psychoneuroses

Using criteria which demonstrate unequivocally the presence of severe hypoglycemia Whipple found islet cell tumors in 27 of 32 patients operated on at the Presbyterian Hospital It is possible that adenomas may have been present in unoperated patients who presented less convincing evidence of hypoglycemia At times it is essential to resort to surgical exploration to establish the diagnosis but even this procedure is not wholly satisfactory since small adenomas lying deep in pancreatic tissue easily escape detection Hypoglycemia resulting from organic disease of the pituitary thyroid or adrenal glands or of the liver usually occurs in association with other manifestations of disease of these structures and consequently presents little difficulty in diagnosis *In any patient exhibiting unexplained hypoglycemia the possibility of factitious hypoglycemia e g self administration of exogenous insulin must be considered*

Treatment The therapy of spontaneous hypoglycemia can be separated into (1) the treatment of the acute episode and (2) the treatment of the underlying cause

The management of the attack depends obviously upon its intensity and its response to therapy Early and intensive treatment of hypoglycemia is of importance to prevent anoxic damage in the brain Frequently 10 gm of sugar orange juice glucose as candy or a glass of milk will relieve the symptoms and raise the blood sugar to a normal level When hypoglycemia is more severe and the patient is unable to swallow 0 5 to 1 mg of epinephrine may be administered subcutaneously as an emergency measure and 10 to 20 gm of glucose should be given intravenously in 25 to 50 per cent solution The injection of glucagon offers little advantage over epinephrine In cases of intractable or frequently recurring hypoglycemia 1000 ml of 5 per cent glucose can be given by hypodermoclysis In these patients it is essential also to give by gavage hourly feedings containing both glucose and milk or a casein autolysate until symptoms have been relieved for some hours When the patient is able to cooperate oral feedings at two hour intervals should be instituted Despite all therapeutic efforts hypoglycemic attacks occasionally have a fatal outcome

The management of the underlying causes is naturally dependent upon the nature of the lesion If the diagnosis is believed to be *hyperinsulinism* due to an organic lesion of the islands of Langerhans surgical intervention should not be delayed since the frequent feedings necessary to ward off attacks often lead to the development of obesity which adds greatly to the difficulties in ultimate surgical treatment Steroids or corticotropin and a high protein diet may be tried to control hypoglycemia of *sarcomas* and other malignant tumors when resection fails

In patients with functional hypoglycemia in whom the symptoms tend to recur just before meals it is advisable to prescribe a diet high in protein and to reduce the intake of sugar This regimen appears to be useful When functional hypoglycemia is associated with a psychoneurosis it is possible that treatment of the latter will reduce the tendency to hypo

glycemia *Idiopathic hypoglycemia of infants* first recognized by McQuarrie is hereditary Patients exhibit hypoglycemia on fasting as do patients with islet tumors The disease regresses with time and can be controlled best with corticotropin

Spontaneous hypoglycemia due to disease of the pituitary or adrenal glands is not benefited significantly by preparations of these glands now generally available although *adrenocorticotropic hormone* administered in early hypopituitarism or cortisone in Addisonian patients with recurrent hypoglycemia may prove useful Treatment is therefore limited to the direct *restoration of the blood sugar* as outlined previously In cases resulting from disease of the liver or biliary tract treatment should be directed toward correcting the underlying disorder

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Obesity

Definition Obesity is that physical state in which the amount of fat stored in the body is excessive It is a symptom which because of its implications and consequences commands the medical consideration accorded serious disease

Incidence Immoderate accumulation of adipose tissue may occur at any age but is more common in middle life Minor degrees of corpulence (10 or 15 per cent above optimal weight) are the rule rather than the exception after the age of thirty years In the United States population of 172 000 000 it is estimated that 15 000 000 are 10 per cent overweight and 5 000 000 are 20 per cent overweight Of these about 4 000 000 are over forty years old Women are more frequently affected than men Extreme obesity or localized distribution of the body fat is uncommon and suggests unusual etiological factors

Etiology A plethora of calories is the only explanation of obesity The law of the conservation of energy applies to the human body as surely as to any other machine which produces heat and performs work When the intake of food whether protein fat or carbohydrate exceeds in caloric value the expenditure as work and heat the excess will be stored in the body tissues Because of the relatively limited capacity of the body to store protein and carbohydrate the greatest part of the excess is *converted into and stored as fat Thus too* much of any type of food is fattening

Pathological Physiology Numerous careful studies have conclusively demonstrated that changes in body weight can be accurately predicted when all metabolic influences are known and measured The apparently paradoxical situation in which weight is maintained temporarily in spite of low caloric intake is explained by transient water retention The immediate cause of obesity is always *a positive energy balance* but there are many ways in which the balance may be tilted toward the positive side Obesity is often divided into two types exogenous and endogenous This classification is not recommended for all corpulence is exogenous (due to an oversupply of food) and likewise endogenous (the reason that the caloric intake is excessive lies within the patient s body)

Although one or more endogenous factors may be present the intake of more food than is necessary is the cause of the excess fat deposit Enforced inactivity from a broken leg does not cause weight gain but the persistence of normal" food habits (now excessive) is chiefly responsible A psychoneurosis may among other symptoms be manifested by gluttony with resultant obesity but a similar psychoneurosis may lead to anorexia and emaciation *The difference is in the food intake*

A positive caloric balance may result from an intake greater than normal or expenditure less than normal or a combination of both these influences Weight is maintained within normal limits in most persons without conscious attention to diet or exercise until the age of thirty or thirty five Aberration from a desirable level of intake or from optimal expenditure of energy may result from either physiological or psychological disturbances or both

Physiological Factors A number of the possible metabolic disturbances have been investigated and many attractive theories have been disproved *Digestion* of food is not more complete nor is *absorption* more *efficient in obese persons* *Lipophilia* of the tissues consisting in an ability to take

up fat more readily or to retain it more tenaciously than normal has not been demonstrated to account for the usual type of generalized adiposity *Local factors* must however be invoked to explain the formation of lipomas the occurrence of lipodystrophy (the commonest type consisting of a lean upper body and obese hips thighs and legs) and the characteristic fat distribution of certain endocrine disorders

A basal metabolic rate lower than normal if coupled with an average normal food intake causes fat storage but *low metabolic rates* account for relatively few cases of obesity The great majority of obese persons have rates within normal limits Persons with hypothyroidism may be overweight if the appetite is good but often the desire for food decreases in proportion to the metabolic rate If the metabolism of food (*the specific dynamic action*) were accomplished with less than the usual expenditure of energy obesity theoretically might result Recent studies indicate no abnormality in this respect in those who become obese The *total metabolism* of obese persons is higher not lower than normal so weight gain cannot be explained by conservation of energy in work or heat production

Certain experimentally produced *destructive lesions of the hypothalamus* lead to the rapid development of obesity in animals Two mechanisms within the hypothalamus appear to regulate food intake if certain lateral centers are bilaterally destroyed aphagia results when the medial control centers are bilaterally destroyed the lateral "feeding areas are freed of their usual regulatory checking action and hyperphagia and obesity result The exact ite of the hunger sensation accompanying hypoglycemia is not yet well understood but studies suggest that glucose levels and perhaps the supply of other metabolites regulate hunger and appetite through the hypothalamic centers Persons with so called pituitary obesity presumably suffer from a hypothalamic disturbance Experimental pituitary destruction does not cause obesity unless the hypothalamus also is injured Epidemic encephalitis may be followed by the development of obesity and in such cases hypothalamic lesions have been found which resemble those known to cause experimental adiposity

Certain *endocrine disorders* may predispose to obesity Frohlich s syndrome characterized by hypogonadism and obesity has been considered the result of *hypopituitarism* but present evidence indicates that the glandular disturbance is not the cause of the obesity but is an associated phenomenon In *adiposogenital dystrophy* the excessive fat accumulation may result from hypothalamic disturbance but its typical distribution is characteristic of hypogonadism which may result from pituitary insufficiency Clinically destruction of the pituitary does not cause obesity but pituitary cachexia (Simmonds disease) In *Cushing s syndrome* there is a peculiar plethoric obesity confined to the head neck and trunk This syndrome originally considered to result from pituitary basophilism is apparently not caused primarily by pituitary disease but by prolonged hypersecretion of the adrenal cortex Similar obesity occurs in some cases of *hyperadrenocorticism* without evidence of pituitary disorder and may be produced by administration of cortisone or related steroid hormones Although a low basal metabolic rate cannot explain the usual type of obesity *hypothyroidism* may be associated with gain in weight partly due to water retention in the tissues and partly to fat storage Functional or organic hypoglycemia (*hyperinsulinism*) is frequently associated with abnormal hunger leading to excessive food intake and obesity Removal or destructive *disease of the gonads* predisposes to obesity there is less tendency to muscular exertion and there is a moderate fall in the basal metabolic rate Many women show such changes and gain weight after the menopause and similar but less evident symptoms often occur in men as sexual activity wanes The adiposity characteristic of hypogonadism involves chiefly the breasts abdomen hips and thighs From these considerations it is apparent that it is inaccurate to speak of endocrine obesity The endocrine disorder does not cause the obesity but may favor its development by increasing food intake or decreasing energy expenditure or both Localization of fat deposits is however specifically influenced by certain abnormalities of the internal secretions

Despite previous popular concepts the majority of obese children show no evidence of endocrine deficiency on the contrary they exceed the average in height and attain earlier sexual maturation

Limitation of energy output in the form of muscular exercise while eating habits remain unaltered causes weight gain and explains the obesity often developing after enforced inactivity following fractures rest treatment of tuberculosis poliomyelitis and other diseases

Obesity occurs more frequently in certain families than in others In animals the *hereditary influence* is clearer than among human beings but even in the latter evidence points to the inheritance of the tendency to obesity

Psychological Factors Some persons enjoy food more than others because of habit or training eat more than they require and become fat The food excess need not be great 15 gm too much of fat or its equivalent in other foods per day will lead to a gain of a pound a month or 12 pounds a year Family custom or imitation of elders often starts the habit During periods of athletic activity or strenuous muscular work habits of eating are often acquired which persist for years after the requirement for the high calorie intake ceases (Normal rats can be trained to eat a whole day s food in one hour such rats like those with hypothalamic damage convert carbohydrate to fat at excessively rapid rates) The habit of overeating frequently is established after illness when a concentrated highly nutritious diet is encouraged Preference for the richer less bulky foods is often part of a behavior pattern dating from early life sometimes started by the misguided anxious or overindulgent parent Some enjoy exercise less and prefer sedentary occupations and will become obese even with an apparently normal diet Such excessive food intake or low energy output if only moderate in degree can hardly be considered pathological for pleasure in eating and avoidance of exertion are universal human traits The common moderate obesity of middle age probably results from the persistence of the dietary habits of youth coupled with an increasing disinclination to muscular effort which in turn is due at least partly to diminution of gonadal secretion The degree of overweight is seldom extreme and reduction by formation of new habits is often easily accomplished

When obesity is extreme psychological influences beyond such relatively normal limits are suggested The majority of persons maintain approximately normal body weight without conscious regulation of food intake Intake is by some mechanism balanced with the caloric requirements Evidently the metabolic processes and nutritional status of the body normally regulate the psychological drives which govern appetite satiety and physical energy These psychological sensations may become deranged so that the usually automatic balance of the intake and outflow of energy is upset Pleasure in eating may become a dominant personality trait The sense of repletion after a meal may require an inordinate amount of food The sensation of physical energy usually expressed in muscular activity may be depressed

When social business or sexual desires are unsatisfied the enjoyment of food often becomes magnified in importance and serves as a substitute Addiction to food like alcoholism is often a symptom of psychological maladjustment Placid day dreaming in which desires are imaginatively fulfilled may take the place of ambitious exertion so that not only is the caloric intake increased but energy expenditure is diminished In addition the resultant obesity makes the satisfaction of social and sexual desires less likely and physical exercise more difficult more discouraging and more fatiguing A vicious circle thus becomes established which favors further increase in the adiposity

Obesity may not only be the result of defensive mental processes but the obese state itself may appear desirable to the psychologically maladjusted person for use as a defensive or offensive weapon It may serve as a defense against undesired contacts or activities for example to avoid sexual advances of an unloved husband or to escape work In a positive direction it may be useful to gain attention and is often used by children to demand solicitous care

Combined Physiological and Psychological Factors In the great majority of cases of obesity both physiological and psychological influences may be discovered For example adiposogenital dystrophy (secondary to hypothalamic disturbance and hypogonadism) leads to weight gain and the psychic reaction to the sexual deficiency favors the substitution of eating for other satisfactions Psychosomatic relationships are also clearly evident when emotional disturbance causes ingestion of carbohydrate foods and then the carbohydrate habit results in regularly recurring hypoglycemia due to functional hyperinsulinism with consequent hunger more carbohydrate ingestion and obesity

Morbid Anatomy A certain amount of fatty tissue is a normal component of the body furnishing important structural support and acting as a storehouse of energy In extreme obesity the subcutaneous fat may be 10 cm or more in thickness and excessive fat deposits occur in the retroperitoneal tissues omentum mesentery perirenal tissues mediastinum and pericar

dium Large deposits may occur in the fascial planes between the muscles and fat infiltration may be found in the pancreas and heart The liver may be enlarged each liver cell containing a large fat vacuole

Symptoms Obesity causes dyspnea and fatigue increasing in proportion with the degree of overweight In extreme cases the bulk of the body may cause such mechanical limitation as to result in almost complete incapacity Flat feet and arthritis of the knees and lower back are common and often serious Maceration and infection of the skin beneath rolls of fat occurs Corpulence increases the probability of cardiac failure in heart disease and exaggerates the symptoms resulting from an impaired circulation

In patients without primary pulmonary or cardiac disease severe obesity may lead to alveolar hypoventilation arterial hypoxemia and hypercapnia These changes result in cyanosis reduced vital capacity secondary polycythemia somnolence pulmonary hypertension and right heart failure Adequate weight loss is accompanied by complete disappearance of this cardiorespiratory syndrome

Diagnosis Adiposity may be obvious from inspection alone but determination of the *ideal weight* and the *degree of obesity* is desirable This may be accomplished within approximate limits by reference to tables or more exactly for each person by calculation from skeletal measurements Use of tables giving *average* weight at various ages and heights is misleading for the optimal weight of an adult remains unchanged but average weights increase in the middle decades The use of the Wood Baldwin tables for desirable weights of boys and girls is recommended (published by the American Child Health Association) and for men and women the tables published by the Metropolitan Life Insurance Company The latter tables take into account not height and age but height and relative size of skeleton or 'body frame

More important in diagnosis than detection of obesity and its severity is discovery of the etiological factors The various possible physiological and psychological disorders must be considered and appropriate methods must be used to investigate the patient s history and habits his physical characteristics and response to special tests Psychiatric study often yields the solution and reveals the obesity as a symptom of a basic maladjustment

Prognosis The prognosis can be treated from two viewpoints (1) What is the likelihood of achieving an approximately normal weight? (2) What influence has obesity upon health and longevity?

1 Whether the obese person will accomplish satisfactory weight loss depends upon the effectiveness of treatment The success of therapy depends upon discovery of the etiological factors and their removal or control The physician must find out why the positive energy balance developed and must know how to reverse the process The patient must understand and cooperate If both roles are not well performed the outlook is poor if they are well performed establishing normal weight is not difficult

2 Obesity if persistent impairs health *and shortens life The hazard of obesity increases* with its degree of severity and with the age of the subject Persons 10 pounds overweight have an increase above the average death rate of 8 per cent when 20 pounds overweight of 18 per cent 30 pounds overweight of 28 per cent 50 pounds overweight of 56 per cent Death from cardiovascular renal disease is 62 per cent more frequent in the obese than in persons of normal weight Cirrhosis of the liver appendicitis biliary calculi and liver and gallbladder cancer occur about twice as often in the obese cerebral accidents and puerperal complications about one and one half times as often Twelve per cent more of the obese die from accidents possibly because of subnormal agility Gallbladder disease is especially frequent in those overweight Obesity predisposes to diabetes especially after age forty The death rate from diabetes is about four times as great in the obese The greater the obesity the poorer the prognosis following surgical operations Resistance to infections such as pneumonia is decreased

Treatment Prevention or elimination of obesity depends upon instruction by the physician and dietitian but the patient must carry out his own treatment Therefore the *patient* must be impressed with the seriousness of the condition and provided with *specific means* to combat it The physician cannot enlist the necessary cooperation of the patient by condemning him for gluttony or laziness every effort should be made to discover the underlying disturbance in each case

Prevention of excessive weight gain is preferable to and easier than treatment Proper eating habits of those predisposed to obesity for any reason and of persons

entering middle age should be established and unless contraindicated moderate regular exercise should be encouraged

Weight reduction may be accomplished by decreasing the food intake by increasing the energy expenditure or both Although the immediate cause of obesity is always a caloric intake in excess of the requirements treatment which consists solely in giving the patient a low calorie diet outline is seldom successful This is because the reasons for the positive energy balance are frequently multiple and successful therapy requires removal of the causes often both physiological and psychological

Treatment may be divided into two phases (1) elimination of etiological factors and (2) getting rid of the excess fat stores For example if hypogonadism is a causative influence use of gonadotropins or gonadal hormones is helpful or if hypothyroidism is a factor thyroid therapy is indicated or if a *psychological difficulty* is expressed in inordinate eating its removal is necessary before the patient can reduce weight by dieting Removal of stored fat may be accomplished by forcing its consumption for the production of body heat and energy To achieve this the caloric intake must be reduced or the metabolism accelerated or both Increase in energy expenditure may be induced by *exercise* when muscular exertion is not contraindicated by such complications as myocardial disease orthopedic disorders and so on Definite amounts of moderate regular exercise such as walking golf and swimming should be prescribed since it not only increases caloric output but improves muscle tone and general health *Desiccated thyroid* will raise the metabolic rate and facilitate weight loss but it should be given only when there is definite hypothyroidism and then only in amounts sufficient to maintain a normal basal metabolic rate Dinitrophenol will accelerate metabolism but is toxic and should never be used

Drugs to induce purging may reduce weight temporarily chiefly through water loss but the treatment of obesity is necessarily a prolonged process and repeated catharsis is ineffective and harmful

Diuresis with weight loss often occurs during therapy with low calorie low salt diets The use of diuretic drugs is usually not advisable unless indicated by the presence of edema

Diet restriction is always necessary to induce weight loss (except in the mildest cases) no matter what caused the obesity An allowance of 35 calories per kilogram of body weight is a maintenance diet for the average moderately active person Limitation to 15 or 20 calories per kilogram of ideal weight provides a satisfactory reduction diet which will permit the patient to follow his usual occupation and to lose 1 or 2 pounds a week For an ideal weight of 70 kilograms (154 pounds) this would amount to 1000 to 1400 calories daily The protein allowance should be liberal (1 to 1 5 gm per kilogram) because of the high satiety value of protein its high specific dynamic action and its importance in protecting tissues and building muscles Carbohydrate should be taken chiefly in the low-carbohydrate bulky fruits and vegetables and should total 0 75 to 1 5 gm per gram of protein The fat intake should be minimal restricted primarily to the eggs and meat necessarily included in the liberal protein allowance and amounting to about 0 5 gm per kilogram of ideal weight A widely applicable diet of this type providing approximately 85 gm of protein 35 gm of fat and 105 gm of carbohydrate (1075 calories) follows 2 glasses of skimmed milk or buttermilk 3 slices of whole wheat bread 1 egg 2 servings of lean meat 1 potato 4 servings of 1 to 8 per cent vegetables (raw cooked or in salads) 3 servings of raw or unsweetened canned fruit The daily food allowance should be divided into three or four meals of approximately equal caloric value omission of meals should be discouraged Such a diet should be adequate in calcium iron and ascorbic acid but if followed for a long time should be supplemented with concentrates of vitamins A and D and the B complex Moderate restriction of water and sodium chloride is advisable for patients who tend to retain fluid

Prescription of a diet does not ensure its observance The patient must be instructed in the principles and details of the diet The causes of excessive appetite must be eliminated if possible and psychological drives encouraging low caloric intake must be substituted pride in appearance desire for physical skills wish to avoid physical disabilities and to prolong life

Dietary instructions should be *written* and must be explicit and detailed

Most essential is *periodic consultation* with the physician to maintain morale provide encouragement record weight loss and improved body measurements and to permit repeated instructions concerning diet and other details of treatment Too often the obese patient is considered medically unimportant and uninteresting is given in

adequate instructions and these only once and then is cast adrift to fight his long and difficult battle alone As in other conditions requiring prolonged therapy dietary control and attention to psychiatric aspects frequent advice from a sympathetic physician is vital In obesity more than in any other common condition rather simple measures can result in great relief of symptoms and prolongation of life

Formal *psychotherapy* is seldom required if prolonged cooperation with an understanding physician can be established More deep seated psychic disorders or habit patterns may require the attention of a trained psychiatrist

Drug therapy in some cases helps to decrease appetite especially amphetamine sulfate 5 to 10 mg one half to one hour before meals usually on arising at 11 A M and 4 P M (not after 4 P M since it causes insomnia)

The physical and psychic effects of successful treatment are usually gratifying Weight reduction often results in correction of menstrual disorders diminution in hypertension decrease in circulatory and cardiovascular strain with relief of dyspnea fatigue and edema decrease in joint pain in the engorgement of venous varicosities in the discomfort and disability from hernia improvement in carbohydrate tolerance and increase in physical and mental efficiency and in enjoyment of the normal pleasures of life

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Atherosclerosis

Definition Atherosclerosis is a disease in which patches of lipid containing material (atheromas) are deposited beneath the intimal surfaces of blood vessels It is not to be confused with senile or involutionary arteriosclerosis in which loss of calcium lipid and protein appear as inevitable consequences of the aging of arteries Its development depends upon causes quite separate from those involved in Monckeberg s medial calcification Pathogenetically as well as anatomically it is distinct from the arteriolar sclerosis which characteristically accompanies prolonged hypertension The distinction is significant because senile arteriosclerosis and medial calcification are not often demonstrably consequential in the production of symptoms while the complications of arteriolar sclerosis although serious differ from those of athersclerosis In older persons however strict separation of the several forms of arterial disease offers difficulty since atheromatous deposits are seen in vessels which have already developed senile alterations which exhibit variable degrees of medial calcification and which may show the characteristic arteriolarsclerosis of concomitant high blood pressure

Incidence Postmortem examinations indicate that in more than 50 per cent of North Americans who die before the age of fifty atheromatous plaques are demonstrable and that among those who die after the age of seventy five more than 90 per cent are moderately or seriously afflicted That the disease does not spare American youth is indicated by studies of soldiers killed in combat in Korea In 40 per cent of men averaging twenty two years of age atherosclerotic plaques of some degree were found in the coronary arteries The disease is so widely distributed as to suggest a defect inherent in mankind Certain it is that conditions otherwise regarded as normal permit extensive formation of atheromatous patches in blood vessels of a large part of the adult population of North America and northern Europe The susceptibility of man is the more remarkable since other species of mammals have not been shown to develop spontaneous atherosclerosis

Etiology and Pathogenesis Although in man the tendency to atherosclerosis appears to be almost universal the rapidity and extent of development of the lesions are modified by a variety of factors *Race* appears to have an important influence on the degree of susceptibility Of people living in the United States Jews are especially prone to the serious effects of the disease Testimony of many observers indicates that in their native habitat Mongoloids African natives and the Tamils of southern India are less affected than the Caucasians of the United States and northern Europe Difficulty is encountered in interpreting the evi

dence concerning some of the supposed racial differences since the influence of other factors such as longevity eating habits and the frequency and thoroughness of postmortem examinations cannot readily be evaluated For instance serious complications of atherosclerosis are rare among Japanese living in their own land but are more frequently encountered among their countrymen in Hawaii and southern California *Familial and hereditary influences* are potent factors in determining the rate at which atherosclerosis develops Families afflicted with hypercholesterolemia and especially those in which the cholesterol concentration is so high and persistent as to produce xanthomatosis tend to develop extensive lesions and serious or fatal complications in early life The degree of atherosclerosis increases with *age* Lipid deposits are seldom seen in the newborn although they may develop as yellow streaks in the aortas of unweaned infants within a few weeks following birth Lesions tend to become more extensive with each succeeding decade a circumstance which is in part the result of accretion of repeated deposits but which may be attributable in some degree to changes in physical and chemical factors in the aging population *Sex* appears to exert a significant influence on the rate of development Women before the menopause seldom suffer from complications of the disease When compared with men of like age they exhibit less atherosclerosis of the coronary arteries and possibly less deposit in the peripheral vessels In older women this outstanding advantage appears to be lost and in the later decades of life there is little difference between the sexes either in the extent and degree of the deposits or in the incidence of their serious consequences

Some *physical factors* favoring the deposit of lipids in arterial walls have been well established The lesions tend to occur earlier and to be more florid in areas of *intimal thickening* They are exaggerated in locations where *syphilis* or other injury to the circulation within the arterial wall has previously occurred That the deposit is to some extent dependent upon a minimum *blood pressure* is indicated by the fact that pulmonary arteries and veins do not become atherosclerotic unless their intraluminal pressure is materially increased by disease In otherwise normal individuals the deposit is greatest at sites in the arterial system where the blood pressure is highest Persistent *hypertension* exaggerates the tendency to atherosclerosis so significantly and constantly that in the past high blood pressure has been regarded as a primary cause of the atheromatous changes

Although physical factors are undoubtedly important in determining the location and extent of lesions the fact remains that atheromas develop widely in arteries that reveal no evidence of preceding structural changes Differences in blood pressure and the anatomy of arterial walls have failed to explain the variation and susceptibility between man and other mammalian species Thus attention has been focused on the possibility that something in the *chemical composition* of the plasma of man makes him more vulnerable than other species A number of factors have been emphasized It has been suggested that the rate and extent of deposit might be dependent upon the cholesterol concentration in the plasma that it might be more influenced by the cholesterol phospholipid ratio that it might depend upon the distribution of lipids between the several lipoproteins of plasma that it might depend upon the actual amount of the lipids combined with beta₁ globulins in the form of beta lipoproteins or upon the concentration of specific forms of beta lipoproteins recognizable in the ultracentrifuge Investigations have shown that in several of these particulars the plasma of man differs from that of nonsusceptible mammals and that the divergence is greatest in physiological states and in diseases which appear to predispose to more rapid and more extensively atheromatous deposit In general observations lend strong support to the chemical hypothesis for the pathogenesis of atherosclerosis although they do not establish any one chemical factor as solely responsible It now seems not unlikely that atheromatous deposits are dependent upon chemical factors operative to some extent in all human adults but grossly exaggerated with familial predisposition and with a variety of diseases

Pathogenetic significance has been attributed to other circumstances There is some statistical evidence that *habitus* is important and that the disease appears earlier and more extensively in mesomorphic persons Heavy indulgence in alcohol over many years has seemed to afford some protection while excessive use of *tobacco* has been urged as a contributing factor to the development or aggravation of complications A low caloric vegetarian diet has been regarded as protective whereas consumption of animal fat has been thought to exaggerate the deposit It has been stated

and contradicted that the obese develop a greater degree of atherosclerosis than the spare Abundant evidence supports the con tention that grossly overweight persons suffer at an earlier age the serious conse quences of the disease

Pathology Atherosclerosis is preemi nently a disease of the aorta and its branches It is minimal or absent in pul monary arteries except in conditions such as mitral stenosis which cause pulmonary artery hypertension It is not seen in the walls or veins except after injury from phlebitis or at sites of arterial venous aneurysms It appears early on the posterior wall of the aorta at the openings of the intercostal arteries and also at the mouths of the coronaries It is more abundant in the descending than in the ascending aorta more evident in the abdominal than in the thoracic portion Atherosclerosis is patchy in its distribution and extensive lesions in vessels of one organ may develop with almost complete freedom from involvement in other parts of the vascular system

The early atheromatous patch consists of cholesterol cholesterol esters phospho lipids and neutral fat together with a con siderable amount of protein When first deposited its composition mimics that of the blood The earliest lesion appears as a yellow linear streak slightly raised above the surface The deposit begins in the deep est part of the intima and the lipid may be seen partly in the intercellular ground substance and partly in the intimal connec tive tissue cells some of which are dis tended with fat to such a degree that they have been called foam cells lipoid cells or lipophages Gradually the fat extends to the surface of the intima The connec tive tissue over the fatty area becomes thickened necrosis may develop in the deeper part of the plaque cholesterol crys tals become more abundant because of the disintegration of cholesterol esters The area becomes calcified and in some in stances somewhat vascularized The amor phous fatty tissue accumulates and at times to an extent which may cause rupture of the intima with ulceration and production of a site favorable to the formation of thrombi In large vessels such as the aorta and its main branches intimal plaques have no appreciable effect on the lumen In smaller vessels such as the coronaries or the arteries at the base of the brain the plaques may accomplish almost complete occlusion and may lead to ischemia or infarction of tissue More often however these accidents are dependent upon throm bosis or hemorrhage on the thickened or ulcerated surface of a narrowed vessel

Clinical Manifestations Extensive lesions may exist for long periods without produc ing clinically recognizable abnormalities The disease need not be widespread how ever to produce serious symptoms A single atheromatous plaque strategically placed may lead to a serious or fatal accident

Clinical manifestations may be limited to fatigue and a diminished capacity to perform mental or physical tasks Localiz ing signs may develop in any part of the body but are usually referable to disturb ances in circulation of the heart brain extremities or gastrointestinal tract

Manifestations Referable to Ischemia of the Heart Muscle In the United States atherosclerosis of the coronary arteries is the most frequent cause of heart disease The most distinctive clinical manifestations are angina pectoris and myocardial infarc tion Pathological experience indicates that 90 per cent of patients suffering from anginal pain exhibit at autopsy obstructive narrowing or occlusion of the main coro nary arteries or their primary branches Causes of myocardial infarction other than atherosclerosis of the coronary arteries are extremely infrequent In the absence of angina pectoris or the signs of myocardial infarction the presence of coronary athero sclerosis even when it has produced exten sive narrowing and multiple occlusions may be clinically unrecognizable Although bundle branch block and other disorders of the conduction system ventricular tachy cardia diminished cardiac reserve and heart failure are common manifestations of the myocardial ischemia of coronary athero sclerosis they occur also in hypertension and other conditions with sufficient fre quency to rob them of diagnostic signifi cance

Manifestations Attributable to Athero sclerotic Disease of the Aorta Even mas sive atherosclerosis of the aorta may be clinically unrecognizable except by roent genographic visualization of intimal calcifi cation Rarely when combined with hyper tension and dilatation of the aortic ring it may contribute to incompetence of the aortic valve In syphilitic aortitis atheroma tous plaques tend to be excessive where the arterial wall and its internal circulation have been damaged by the spirochete Sac cular aneurysms are not attributable to atherosclerosis although their walls may contain many atheromatous plaques Dis secting aneurysm which was formerly at tributed to channeling of the blood beneath

fractured calcified patches of atherosclerosis in the presence of hypertension is now usually ascribed to cystic degeneration of the media In the abdominal aorta repeated and progressive thrombosis at the site of atheromatous patches may occlude the great vessel sufficiently to produce peripheral ischemia and manifestations of the Leriche syndrome

Clinical Manifestations of Cerebral Atherosclerosis Together hemorrhage and thrombosis of cerebral vessels constitute 90 per cent of all cerebral vascular lesions In both processes atherosclerosis is significantly implicated for it is recognized as the most frequent cause of cerebral thrombosis and traditionally hemorrhage has been thought to result from the rupture of an atherosclerotic vessel in the presence of hypertension Furthermore before actual blockage or hemorrhage occurs progressive occlusion of vessels leads to ischemia with patchy degeneration of cortical cells and nerve tracts and disseminated areas of atrophy Actual obstruction with or without thrombosis leads to small or large areas of softening Numerous small lesions as well as larger ones may result in paralysis or in mental deterioration which clinically overshadows the loss in motor function They cause diminution in intellectual capacity impaired memory especially for recent events and names emotional instability addiction to reminiscence with more or less confabulation The victim becomes self centered hostile and sometimes paranoid with loosely constructed delusions Actual dementia is not uncommon Progressive intramural clot formation on atheromatous patches in the internal carotid arteries by interfering with cerebral circulation may cause transient paralyses and unilateral blindness or may simulate neurological defects more frequently caused by disease of the cerebral vessels

Manifestations of Atherosclerosis of Peripheral Arteries Atheromatous disease is by far the commonest cause of arterial occlusion in the legs Except in diabetics symptoms referable to its presence are uncommon before the age of fifty five In the arms serious impairment of circulation from atherosclerosis is not frequent and the calcification which is so often demonstrable in the radial ulnar and brachial arteries of older persons is usually attributable to medial rather than intimal disease Obliterative lesions in the terminal branches of the posterior tibial and dorsalis pedis arteries produce symptoms which in their early stages consist of paresthesias nocturnal cramps weakness and chilliness of the legs and feet Later faint discoloration of the ends of the toes may be followed by more serious circulatory disturbance or by dry or moist gangrene In many patients the most troublesome symptom is intermittent claudication which consists of cramping pain that appears with walking and subsides with rest This may develop before the signs of complete arterial occlusion are apparent Prominent physical signs are lack of pulsation in the peripheral arteries blanching on elevation of the foot with slower than normal return of color with dependency The veins remain collapsed for some time

Manifestations of Atherosclerosis of the Mesentery Vessels Digestive disturbances including achlorhydria intestinal atony and constipation which are frequent in the aged have been attributed without convincing proof to the impaired circulation and ischemia of atherosclerosis Thrombosis of the mesenteric arteries like that of the coronary and cerebral vessels may depend upon the formation of an intraluminal clot at the site of an atherosclerotic patch

Diagnosis As yet there is no adequate clinical or laboratory means of estimating the degree and extent of atherosclerosis or even of recognizing its presence Lesions may be suspected because of the visibility by roentgenographic examination of calcified lesions in the aorta and its main branches Tests of tolerance to exercise and response to deprivation of oxygen ballistocardiographic observations and electrocardiographic studies may permit the inference that the coronary circulation is insufficient Careful measurement of the pulsations in the extremities may indicate defects which are usually ascribable to atherosclerosis Unfortunately even with the use of all of these tests the existence of atheromatous plaques often is not established until serious complications have already developed

Treatment In considering the treatment several objectives may be kept in mind (1) It would be desirable to limit or prevent the deposit of lipids or to cause the disappearance of lesions already formed (2) It would be an advantage to control hypertension which is thought to accelerate the deposit and to favor rupture of atherosclerotic vessels (3) Most desirable of all would be the prevention of intraluminal clotting which is responsible for a large part of the mortality and morbidity of the disease

Criteria for judging the degree to which

any one of these desirable objectives is achieved are unreliable Since we cannot satisfactorily recognize the location and extent of atheromatous lesions we cannot tell whether they are affected by therapy Under the best circumstances judgment concerning efficacy of management would require statistical analysis of an immense experience

A vast number of remedies have been suggested and tried Of the more recent ones a word may be said Neither the efficacy nor the rationale for administration of choline methionine lipocaic and inositol has been established The use of heparin recently suggested with hope deserves further study As yet its efficacy in accomplishing any of the objectives of treatment has not been proved It has been shown that the administration of estrogen can modify the cholesterol concentration and abnormal lipid pattern of survivors of myocardial infarction to a degree which in many cases amounts to reestablishment of normal chemical conditions It has not been demonstrated that the administration of a female sex hormone inhibits or prevents the development of atherosclerosis or exercises any influence on the incidence or severity of its complications Side actions of estrogens chiefly impotence and gynecomastia are so undesirable as to preclude their extensive therapeutic trial

In patients who have suffered myocardial infarctions carefully controlled anticoagulant therapy has aided in the prevention of still more serious complications Success in this situation has suggested the more extensive use of anticoagulants in the prophylaxis of thrombosis in those who appear to be especially threatened by the degree and location of their atherosclerosis

In recent years chief attention in the treatment of atherosclerosis has been focused upon the use of diets with chief emphasis on restriction of cholesterol fat and caloric intake Extensive trial of diets low in cholesterol alone has failed to show crucial changes in the cholesterol concentration of the plasma or in most of the essentially pathological features of lipid composition in persons especially susceptible to the development of atherosclerosis There is more convincing evidence that limitation of dietary fat might be beneficial Studies by Keys on population groups in various parts of the world have shown a close correlation between the percentage of total dietary calories derived from fat concentration of cholesterol in serum and incidence of myocardial infarction Those people who consume the most fat show the highest concentration of serum cholesterol and the highest incidence of coronary heart disease Myocardial infarction appears to be rare among people who habitually take less than 20 per cent of their total calories in the form of fat Observations by Ahrens Kinsell and Malmros suggest that the form as well as the total amount of fat may be important in the pathogenesis of atherosclerosis Substitution of equicaloric amounts of corn oil for dairy fat in a balanced diet is predictably accompanied by a reduction in concentration of serum cholesterol These recent dietary studies have definite therapeutic implications Even in their present incomplete state they suggest the advisability of both quantitative and qualitative modification of fat intake for persons especially predisposed to atherosclerosis and its complications As yet they are not sufficiently conclusive to permit recommendations for radical reform in the national diet While we wait for more complete data it is possible however to offer some general advice

It is no new doctrine that gluttons have a relatively high morbidity and mortality from vascular disease or that there is greater average longevity and relative freedom from vascular accidents among the spare and the frugal More recent evidence has strengthened this traditional impression It is stated with statistical support that the obese have a greater incidence of hypertension and that atherosclerotic plaques develop earlier and more abundantly in the overfed Some evidence has been presented that life expectancy may be increased by correcting overweight This circumstantial evidence seems to indicate that a low fat low but adequate caloric diet may be advised with the expectation of partial protection against the rapid development of the complications of atherosclerosis Since man is an atherosclerotic animal and since atheromas form to some degree in most people in middle and later life this advice need not be limited to those already obese or to those who have disclosed the obvious presence or complications of atherosclerosis

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Xanthomatosis

Definition Xanthomatosis as defined in this section includes only those conditions in which deposits of lipid in tissues are dependent upon or accompanied by abnormally high concentrations of lipids in the blood Not included are several clinical states which are sometimes given the name of xanthomatosis and are characterized by lipid containing histiocytes or reticular endothelial cells but which develop without perceptible hyperlipidemia (See Niemann Pick s Disease Hand Schuller Christian Disease)

Lipid accumulation may consist chiefly of cholesterol (hypercholesterolemia) or of neutral fat (hyperlipemia) and xanthomata may develop in either condition Chemically separation of the two states *cannot be sharply made since many cases* of hypercholesterolemia exhibit moderate increase in the plasma concentrations of neutral fat and most cases of hyperlipemia have higher than normal plasma concentration of cholesterol Attempt at distinc*tion is useful however because of differ*ences in clinical manifestations

Etiology and Pathogenesis *Hypercholesterolemia* The mean cholesterol concentration for young normal adults is about 200 mg per 100 ml with a rather wide range from 120 to 280 mg per 100 ml In older normal persons of both sexes the mean as well as the maximum concentrations are moderately increased Although there are large *differences between members of a* group the range of concentration in each individual is seldom more than ± 15 per cent under a considerable variety of life situations Hypocholesterolemia normocholesterolemia and hypercholesterolemia are relative terms and the dividing line between the normal and the pathological is entirely arbitrary *In this* discussion we have set 300 mg per 100 ml as the upper limit of normal but with the suspicion that values below this level may be consequential in the tendency to deposit of lipids in tissues

Hypercholesterolemia has been observed *under a variety of conditions* but may be classified rather simply as *familial* or idiopathic and *acquired* either in the course of diabetes nephrosis or myxedema or as a consequence of hepatic and biliary tract disease

By far the commonest cause both of excessive concentration of cholesterol in plasma and of xanthomatosis is *essential familial hypercholesterolemia* That it is hereditary is attested by many observations of family groups in whom hypercholesterolemia xanthomatosis premature atherosclerosis and coronary heart disease are so frequently encountered as to be considered parts of the same genetic defect Active discussion in the literature continues on the question of whether inheritance can be explained on the basis of a simple dominant or an incompletely dominant gene

Hypercholesterolemia from secondary causes is seldom sufficiently severe or prolonged to cause deposit of lipids in the *skin When these do appear* they take the form of eruptive xanthoma and usually consist of small papules pinhead to pea size subcutaneously located on the trunk and extremities and surrounded at their inception by hyperemic halos In the arteries extensive deposit of lipids and the clinical complications of atherosclerosis may ac*company both diabetes and nephrosis* In myxedema the pathological evidence of more than usual atherosclerosis is less convincing although relative frequency of angina pectoris in this condition has been noted

*The hypercholesterolemia and xanthoma*tosis which accompany hepatic and biliary *disease is seen most often in cases* of long standing biliary cirrhosis Higher than normal concentrations of plasma cholesterol are also frequently encountered in a variety of obstructive lesions of the biliary tract but seldom lead to xanthomatosis of the skin or tendon sheaths In these conditions clinical complications of atherosclerosis are rare although superficial deposits of lipids have been noted in the postmortem examination of the aorta and the endocardium

Hyperlipemia Like hypercholesterolemia the excessive accumulation of neutral fat in the blood may be due to primary or secondary causes It may be simply classified as (1) essential familial hyperlipemia and (2) acquired from nephrosis diabetes von Gierke s disease chronic pancreatitis or a variety of miscellaneous conditions

The family disease is regarded as a rarity

Only a few cases have been recorded Since its presence does not interfere with the maintenance of apparently good health over long periods there is reason to think that it is commoner than a review of the literature might indicate Acquired hyperlipemia is seen more frequently It is a part of the nephrotic syndrome where it is always associated with hypercholesterolemia In a few diabetics hyperlipemia may be extreme and when present is accompanied by greater than normal concentration of all other lipid components Xanthomatosis accompanying hyperlipemia less often involves the tendon sheaths and may take the form of the eruptive xanthoma that is seen in acquired forms of hypercholesterolemia The lesions appear to represent a spillover from the hyperlipemic plasma into highly vascularized tissue Similar forms have been occasionally noted in association with von Gierke s disease and in association with chronic pancreatitis

Pathology The lesions of xanthomatosis tend to be quite similar pathologically regardless of location There is a deposit of lipid and in the hypercholesterolemic families chiefly of cholesterol in subcutaneous and cutaneous tissues tendons and aponeuroses Cholesterol crystals may be evident Connective tissues containing fat and variously called xanthoma cells foam cells or lipophages tend to accumulate In some of the lesions there are giant cells (Touton cells) which contain several nuclei in an almost complete circle around an opaque cytoplasm The lesions are most easily recognized in the skin and tendons but those which develop in the structure of internal organs such as the heart and arteries do not differ materially from the superficial lesions In the eruptive xanthomas much of the lipid is extracellular foam cells are not numerous giant cells are absent little granulation tissue is seen

Chemically there are significant differences in lipid distribution in plasma of the several forms of xanthomatosis In both familial hypercholesterolemia and familial hyperlipemia cholesterol phospholipid ratios exceed unity and lipids are concentrated in lipoproteins formed from normal $beta_1$ globulins In xanthomatosis accompanying primary biliary cirrhosis concentration of phospholipid is twice that of cholesterol and both are combined with globulins in the form of abnormal beta lipoproteins

Clinical Manifestations In many cases both of hypercholesterolemia and hyperlipemia clinical recognition must depend solely upon chemical tests unsupported by any obvious symptoms or physical signs The condition of the patient during life may disclose no evidence of the underlying defect or its anatomical damage

Xanthomatosis has been noted most often and in its most obtrusive clinical forms in association with familial hypercholesterolemia although other forms of hypercholesterolemia and hyperlipemia may mimic the clinical picture of the familial disease The lesions are various and have been given many names

Xanthelasma is a term used to indicate collections of fat and cholesterol in the eyelids Although these are frequent accompaniments of hypercholesterolemia and are occasionally seen in association with hyperlipemia it is important to remember that the lesions may be present in patients who exhibit no chemical defects *Arcus senilis* in relatively young people like xanthelasma is a frequent accompaniment of hypercholesterolemia but may develop in people as in the Eskimos in whom no chemical defect in the plasma can be demonstrated *Xanthoma planum* is the term reserved for flat or slightly raised lipid deposits seen in many parts of the body but with special frequency in the creases of the palms in the folds of the elbows in the creases below the breasts and in wrinkles or folds elsewhere *Xanthoma tuberosum* is a name given to nodular lipid deposits in the skin It appears in many places but may develop floridly on the buttocks elbows knees and hands *Xanthoma tendinosum* is a term used to describe hard nodules of lipid deposits in the tendon sheaths of hands forearms ankles and many other sites

It is to be noted that these different forms and localizations of deposits do not represent separate diseases On the contrary all of them may be evident in the same individual The distinctions are not qualitative but are used entirely for descriptive purposes

Vascular Involvement Those who suffer from familial hypercholesterolemia and xanthomatosis may deposit cholesterol and develop collections of foam cells or lipophages beneath the intima of blood vessels and occasionally beneath the endocardium These lesions cannot be strictly differentiated from the atheromatous patches which are found in persons who have normal concentrations of cholesterol in the plasma They are notable chiefly because of their development in younger persons and because of their greater degree and extent The formation of xanthomas in the vascular system is usually localized to blood

vessels and chiefly to the aorta and its branches with frequent and early involvement of the coronary arteries The deposits may be seen in pulmonary arteries and in a few cases have implicated the endocardium with or without involvement of the aortic mitral and pulmonary valves The evidence of ischemia scarring and infarction of heart muscle is frequently encountered in these patients even in youth Members of such hypercholesterolemic families often exhibit symptoms and signs of heart disease at an early age Angina pectoris is frequent and was noted in one child at the age of four Several sudden deaths in children have been recorded

In idiopathic familial hyperlipemia the deposit of lipids may not be limited to the formation of superficial xanthomas Hepatomegaly splenomegaly and enlargement of lymph nodes have been recorded Foam cells have been found in biopsy specimens of the liver spleen lymph nodes and bone marrow Abdominal pain variously ascribed to acute swelling of the liver and spleen and to pancreatitis has been frequent Glycosuria of mild degree not influenced by the administration of insulin has also been reported A relationship of familial hyperlipemia to atherosclerosis has been less firmly established because of the paucity of autopsies Premature coronary atheroma has been observed and recent reports have emphasized the coincidence of angina pectoris and myocardial infarction The single autopsied case in an infant failed to show deposit in arteries Recent reports of idiopathic familial hyperlipemia however have emphasized the coincidence of angina pectoris and myocardial infarction

Treatment In familial hypercholesterolemia the course of the disease and the development or persistence of superficial xanthomas are but slightly influenced by therapeutic measures It cannot be shown that the cholesterol concentration of the blood is materially diminished by removing cholesterol from the diet Even low fat low caloric diets seem to have little effect on the chemical constitution of the blood The administration of estrogens in most cases is followed by changes in the direction of normal plasma values In no case of xanthomatosis however has estrogen accomplished complete restoration of a normal pattern

In acquired hypercholesterolemia the chemical defects of the plasma as well as the xanthomatoses may be favorably influenced by specific measures This has been particularly dramatic with the use of insulin in diabetic xanthomatosis and with the administration of thyroid substance in the rare cases in which xanthomas develop in the course of myxedema

The possibility of modifying conditions in essential familial hyperlipemia offers more encouragement In this condition it appears that neutral fat accumulates in the blood partly because of a delay in the removal of metabolism of ingested fat Spacing of fat ingestion with restriction for intervals of 24 hours or more has in some cases produced material reduction in the concentrations of neutral fat in the plasma The administration of insulin is successful in controlling the hyperlipemia of diabetes but is ineffective in idiopathic familial hyperlipemia

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Carcinoid Syndrome

(*Carcinoidosis*)

Carcinoid (argentaffinoma) is now known to be an endocrine tumor which produces the pharmacologically active agent serotonin (5 hydroxytryptamine) Lembeck was the first to find large amounts of serotonin in both primary and metastatic carcinoid tumors At the same time (1953) Waldenstrom and others described a bizarre clinical syndrome in patients with metastatic (malignant) carcinoid The various manifestations of the syndrome including cyanosis flushing asthma diarrhea and valvular heart disease appear to result from secretion of serotonin by the tumors and a disturbance in the metabolism of tryptophan Over 100 cases of this disorder have been diagnosed since the original descriptions

Morbid Anatomy Malignant carcinoid usually develops from a small primary lesion of the ileum Hepatic metastases are found in advanced cases and ovarian metastases are frequent in the female More distant metastasis may occur particularly to lung and bone The tumors are yellow in color firm on section and consist of epithelial cells set in a fibrous stroma Intracellular granules giving the chromaffin argentaffin reactions reflect origin of the tumor from the enterochromaffin cells of the intestinal mucosa

Associated pathology is found primarily in the skin and right side of the heart Greatly dilated capillaries and small veins are seen in the skin representing telangiectasia during life Fibrosis of the right atrial and ventricular endocardium may involve the valve leaflets and chorda tendineae to produce pulmonic stenosis tricuspid stenosis and tricuspid insufficiency alone or in combination Cardiac involvement has not been observed in the absence of hepatic metastases

Clinical Features A series of baffling illnesses extending over a period of years is typical coinciding with slow growth of the tumor Current concepts are derived largely from study of advanced cases The clinical features may be listed as follows

Vasomotor The most common and often the earliest manifestation is paroxysmal erythematous flushing of the face and neck Remarkable changes in color may be observed within a few minutes ranging from bright red to violaceous to blanching white Facial and periorbital edema tachycardia hypotension and increased respiratory and intestinal distress may occur with severe flushing Precipitating stimuli include emotional upsets defecation physical activity and manipulation of the tumors After several years miliary and gross telangiectasia may develop and give an appearance of cyanosis in the absence of arterial O unsaturation

Gastrointestinal There is usually a long history of abdominal discomfort in association with recurrent attacks of diarrhea Nausea and vomiting develop with frequent or prolonged flushing Hyperperistalsis is often apparent at the bedside Although the primary tumor is usually silent hepatic metastases frequently undergo necrosis leading to episodes of abdominal pain with fever and leukocytosis The hepatomegaly may become massive but hepatic function as measured by the usual tests is often well preserved and alterations in the tests are nonspecific An increased incidence of peptic ulcer also has been noted

Cardiopulmonary Cardiac involvement is a late manifestation and occurs in about 50 per cent of far advanced cases Right heart failure may supervene in association with pulmonary and tricuspid valve lesions However dependent edema is common even in the absence of cardiac disease Clinical and laboratory findings relating to the heart are comparable to those seen in similar valvular lesions of rheumatic or congenital origin and vary with the severity of involvement Some patients have attacks of dyspnea and wheezing indistinguishable from bronchial asthma Others experience constricting sensations in the chest and recurrent paroxysms of coughing

Nutritional Loss of weight occurs intermittently but is progressive Cutaneous lesions of pellagra have been encountered in several cases Hypoalbuminemia is a frequent finding

Pathological Chemistry and Physiology The major depot of serotonin in the body is the gastrointestinal mucosa Smaller amounts are found also in the brain and blood platelets This amine is derived from the essential amino acid tryptophan and is metabolized to 5 hydroxyindoleacetic acid (5HIAA) which is excreted in the urine (see Fig 71) In patients with malignant carcinoid the tumor is the major body depot of serotonin and generally contains 1 0 to 3 0 mg per gm Blood levels of serotonin are elevated to 0 5 to 3 0 micrograms per ml compared to normal values of 0 1 to 0 3 microgram per ml and the urinary excretion of 5HIAA is greatly elevated usually being 50 to 600 mg per day compared to 2 0 to 10 mg per day in normal persons As much as 60 per cent of dietary tryptophan may be deviated into the serotonin pathway by the tumor

HO— (indole) —C(H)(H)—C(H)(H)(NH$_2$)

5-HYDROXYTRYPTAMINE
(Serotonin)

↓ Amine Oxidase

HO— (indole) —C(H)(H)—COOH

5-HYDROXYINDOLE ACETIC ACID
(5HIAA)

Fig 71

whereas normally only about 1 per cent is metabolized in this manner This diversion of tryptophan leaves less available for the formation of other substances such as niacin and protein

The pharmacological effects of serotonin on smooth muscle account for the vasomotor disturbances hyperperistalsis and bronchoconstriction The acquired lesions of the heart are probably also on a chemical basis but have not been produced experimentally Because of the abnormality of tryptophan metabolism in patients with malignant carcinoid decreased food intake and loss of nutrients by diarrhea which would not significantly affect a normal person may lead to the development of pellagra and protein deficiency

Diagnosis The syndrome is easily recognized when fully manifest However it is important to realize that any single sign or symptom may be the sole or predominant evidence of functioning carcinoid The diagnosis is established by a simple qualitative test for increased excretion of 5HIAA in the urine Values above 15 mg per day are sufficiently high to suggest the diagnosis of carcinoid The ingestion of a few bananas may result in false positive chemical diagnosis since a single banana contains about 4 mg of serotonin

Prognosis Patients with this disorder succumb eventually to nutritional cardiac or hepatic failure

Prevention and Treatment Surgical extirpation of tumor offers the only definitive means of ameliorating symptoms and prolonging life Early diagnosis and inspection of the terminal ileum during routine abdominal surgery with excision of primary lesions offer the best means of prophylaxis An adequate diet and vitamin supplements including niacin are indicated Other medical therapy constitutes the treatment of symptoms and complications Serial measurements of urinary 5HIAA afford a unique method of following progression of the disease or judging the effectiveness of attempts to eradicate the tumor

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The Lipomatoses

The term "lipomatoses" refers to a group of unrelated local abnormalities in fat distribution to be distinguished from systemic disorders of fat metabolism The most common of these abnormalities are *lipomas* slow growing and ordinarily discrete single or multiple benign tumors arising usually from the subcutaneous fat of the shoulders back neck or proximal half of the extremities If tender large or unsightly the lipomas may be excised Interstitial visceral thoracic abdominal and nervous system lipomas also occur A painful form of multiple circumscribed subcutaneous lipoma or neurolipoma is designated *Dercum s disease* or *adiposis dolorosa* *Sclerosing lipogranuloma* is the result of trauma local ischemia and necrosis of fat deposits with infiltration and fibrosis of the surrounding tissue Localized atrophy or spongy hypertrophy of fat may occur at the site of insulin injections *insulin lipodystrophy*

Lipomatosis may be more diffuse symmetrically involving the neck (*"fat neck" Madelung s neck*) to form large disfiguring masses which sometimes extend down over the shoulders and arms or are occasionally segmentally distributed on the thorax In women a common form of symmetrical subcutaneous deposition of excessive fat in the buttocks and legs with more or less dependent edema has been designated *lipedema*

Progressive Lipodystrophy (Barraquer Simmons Disease) Progressive lipodystrophy is a disorder characterized by symmetrical and slowly progressive loss of subcutaneous fat from the face in more severe cases also from the neck arms thorax and abdominal wall with preservation or increase in the fat of the lower part of the body Extensively affected patients present a bizarre appearance of emaciation of the upper portions of the body particularly of the face with contrasting pronounced

obesity of the hips buttocks and legs The cause of the disease is not known

The onset commonly is between the ages of four and eight young girls being chiefly affected but the disorder may develop in adults The rate of progressive involvement varies from one or two years to over a decade but arrest may occur at any stage The muscles hair and sweat glands of affected areas are spared Apart from weight loss and emotional disturbances attending disfigurement there is usually no associated abnormality or incapacity There is no known treatment

Intestinal Lipodystrophy (Whipple s Disease) As described by G H Whipple in 1907 this disorder is characterized by gradual loss of weight and strength stools consisting chiefly of neutral fat and fatty acids indefinite abdominal signs and a peculiar multiple arthritis" The underlying pathological findings include a striking lipogranulomatosis of enlarged mesenteric lymph nodes and the presence of large foamy macrophages filled with an unidentified glycoprotein in the tunica propria of the small intestine cystic dilatation of the mesenteric lymphatics may also occur These morphological abnormalities induce or reflect a malabsorption syndrome resembling sprue

The etiology is obscure The impairment in intestinal absorption particularly of fat at first suggested a metabolic or morphological defect specifically of the cells of the intestinal mucosa but the accompanying widespread systemic involvement and the presence of an abnormal glycoprotein in the serum have subsequently suggested the possibility of a more general metabolic defect Puite and Tesluk have described familial occurrence of the disorder and imply genetic transmission

The disease has a predilection for males usually between the ages of thirty and sixty five The onset is insidious usually with diffuse abdominal discomfort and intermittent diarrhea the stools later becoming bulky frothy and foul smelling and containing large amounts of neutral fat and fatty acids Sometimes the disease is ushered in with bouts of migratory polyarthritis which may indeed dominate the picture for several years Intermittent fever hypotension hypochromic anemia lymphadenopathy chronic cough hypocholesterolemia hypoalbuminemia and edema are common accompaniments Ascites (sometimes chylous) and fibrous polyserositis may occur Occasionally there is pronounced pigmentation of the skin simulating Addison s disease in the late stages tests for adrenocortical function however give essentially normal results X rays show a typical "deficiency pattern" of the small bowel The glucose tolerance curve is normal or flat free acid in the gastric contents is diminished or absent pancreatic secretion is preserved

The diagnosis is most securely established by intestinal biopsy but peripheral node biopsy may suffice to demonstrate nests of macrophages giving a positive periodic acid Schiff stain indicative of abnormal deposits of glycoprotein The serum mucoprotein level may be substantially increased

The course is protracted and with spontaneous remissions characterized by progressive weakness and weight loss terminating in extreme debility and death usually within five years of onset Treatment is supportive and symptomatic Corticotropin and corticosteroids induce amelioration of symptoms in many cases and should be given a protracted trial

Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber Christian Disease) This disorder in its most typical form is characterized by recurring febrile bouts associated with the appearance of crops of subcutaneous fatty nodules which are usually tender The cause of the disease is not known Necropsy findings indicate that the underlying abnormality may be not an entirely local disturbance confined to the panniculus but a more generalized disorder of fat metabolism Kennedy and Murphy believe that the changes in adipose tissue are due to ischemia secondary to thrombosis or endarteritis of small vessels with subsequent necrosis of fat cells and infiltration by macrophages and mononuclear cells Weber found that administration of iodides could produce the manifestations in susceptible persons but in most cases there is no history of exposure to iodides Similar manifestations have been produced by trauma which may be minimal and by repeated subcutaneous injections and local application of cold There is no convincing evidence of an infectious etiology

The earliest morbid changes in the panniculus appear to be accumulations of lipophages often associated with periarteritis and arteriolitis Central areas of softening due to fat necrosis and edema then appear along with increased numbers of fat laden macrophages lymphocytes large mononuclear cells and sometimes many polymorphonuclear cells Late lesions show a decrease in necrotic material and inflam

matory cells with more or less fibrous tissue replacement Similar changes may involve fat deposits in addition to those in the subcutaneous layers—for example pancreatic adipose tissue and omental mesenteric peripelvic periadrenal and epicardial deposits Moreover extensive fatty infiltration and central necrosis of the liver with hemorrhage occur apparently quite regularly Fatty and hydropic degeneration of the pancreas and adrenal cortex have been described as have fat emboli in the lungs

The disorder has been described in patients ranging in age from two to sixty four years Females appear to be somewhat more frequently affected Prodromal symptoms of malaise fever sore throat or arthralgia often precede the onset of fever and the appearance of nodules Leukopenia is the rule and may be marked although some cases have shown leukocytosis Joint and muscle pains sometimes are generalized and severe

The nodules appear most frequently on the thighs they also appear on other portions of the legs on the arms and trunk but rarely on the buttocks breast face hands and feet They are usually multiple vary in diameter from about 1 to 10 cm and are apt to be tender and sometimes spontaneously painful The overlying skin may be inflamed A nodule occasionally may rupture exuding turbid fatty material which yields no bacterial growth on culture Internal fat deposits also may be involved giving rise to obscure febrile episodes and abdominal pain

The course is protracted and marked by remissions and exacerbations There is no satisfactory treatment although improvement of uncertain duration has been ascribed to sulfapyridine and penicillin ACTH and cortisone have been tried but have proved generally disappointing

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Amyloidosis

Definition Amyloidosis is a disorder characterized by the deposition in various tissues of amyloid a difficultly soluble protein containing sulfated mucopolysaccharides of which the most distinctive is heparitin sulfate (Karl Meyer) Variants of amyloid are often referred to as paramyloid

No satisfactory classification of the several categories of amyloidosis is yet possible The most commonly employed scheme lists primary (systemic) amyloidosis (which occurs in familial and sporadic forms) secondary (parenchymatous) amyloidosis amyloidosis associated with multiple myeloma and localized amyloid tumors The distinction between primary and secondary amyloidosis however often is not sharp because of difficulties in evaluating the provocative role of minor suppuration (as in the lungs or kidneys) and the overlapping of organ and tissue distribution Further some cases designated primary amyloidosis probably are instances of occult multiple myeloma In any event primary" amyloidosis presumably is a manifestation of some obscure underlying metabolic disorder and in this sense is really "secondary"

Etiology *Secondary amyloidosis* classically is related to chronic suppuration notably protracted tuberculous involvement of the lungs or bone chronic osteomyelitis due to pyogenic organisms lung abscess or bronchiectasis It occurs also as a complication of many other conditions associated with tissue destruction and infection including malignant tumors (notably hypernephroma) Hodgkin s disease chronic ulcerative colitis and regional ileitis with fistulation rheumatoid arthritis chronic pyelonephritis and paraplegia with suppurating decubitus ulcers and urinary tract infection occasionally also in association with plasmacytosis and hyperglobulinemia in drug sensitivities In recent years owing to the advent of effective antibiotics these latter associations with secondary amyloidosis have indeed superseded in frequency the classic occurrence with tuberculous and pyogenic infections of lung and bone

In view of the protein nature of amyloid and its not infrequent appearance in animals with prolonged hyperglobulinemia due to hyperimmunization or sodium caseinate administration some investigators have related secondary amyloidosis to a disturbed protein metabolism associated

with suppuration and tissue breakdown The evidence for this relationship is not clear however and further investigation is needed

Primary systemic amyloidosis is not ordinarily associated with chronic infection or other overt disorder and its origin remains obscure The familial form is characterized by the presence of an abnormal α globulin component in the plasma which appears to be a lipoprotein (Rukavina *et al*) It has been suggested that the deposits of amyloid in the tissues may be derived from this and other abnormal proteins which have been discovered in the plasma of patients with amyloidosis

The incidence of amyloidosis in *multiple myeloma* varies in different series averaging about 15 per cent Magnus Levy stressed derivation of the amyloid from Bence Jones and related abnormal proteins in multiple myeloma but most cases with extensive amyloidosis do not have conspicuous hyperglobulinemia

Localized amyloid tumors occur as isolated growths chiefly in the larynx trachea and bronchi A rare form limited to the skin has been described (lichen amyloidosis) There is no clue as to etiology

Morbid Anatomy The spleen kidney liver and the cortex of the adrenal glands are the most common sites of *secondary amyloidosis* these organs characteristically being enlarged and firm the involved areas homogeneously infiltrated and of waxy pallor Lymph nodes pancreas gastrointestinal tract prostate thyroid and other organs may also show involvement Microscopic examination indicates a predilection for the walls of capillaries and arterioles earliest deposition occurring beneath the endothelial cells in arterioles extending into the media In the spleen infiltration of amyloid begins in and around the malpighian bodies giving rise to the typical sago spleen in the liver earliest involvement is subsinusoidal in the kidney amyloid first appears subendothelially in the glomerular capillaries beneath the epithelium of Bowman s capsule and occasionally in the tubular epithelium beneath the basement membrane In all organs accumulation and expansion of these deposits in blood vessels and reticulum fibers lead to compression and atrophy of the tissue parenchyma until in advanced cases much of the substance may be composed of amyloid

Iodine (Lugol s solution) imparts a deep brown color to secondary amyloid deposits upon addition of sulfuric acid a dark blue color forms hence Virchow's designation of the substance as amyloid (starchlike) Congo red and eosin give an intensely pink color van Gieson s stain a yellow or brownish color periodic acid Schiff stain a bright red Amyloid stains metachromatically with methyl violet and crystal violet These reactions are consistently obtained in secondary amyloidosis as encountered in man and upon them rests the ultimate diagnosis

In *primary systemic amyloidosis* the sites of predilection are cardiac skeletal and smooth muscle initially involving the interstitium and progressively compressing muscle fibers with atrophy and replacement by amyloid The myocardium characteristically is extensively involved with cardiac enlargement Macroglossia is common The smooth muscle of many medium sized and small blood vessels throughout the body is usually selectively involved Skeletal musculature including the diaphragm and the smooth muscle of the gastrointestinal tract also the skin may be diffusely affected The liver spleen kidney adrenal gland lung lymph nodes peripheral nerves joints bone marrow and other tissues are more commonly involved than is generally stated The skin may be diffusely infiltrated particularly about the head and neck hands and nails often with local hemorrhages or translucent papules and plaques of the skin and mucous membranes may appear Staining reactions with iodine Congo red and the metachromatic dyes are often erratic apparently because of variations in chemical structure

In distribution and erratic staining characteristics the amyloid deposits in *multiple myeloma* resemble primary more than secondary amyloidosis

Symptoms and Signs The onset and progression of amyloid disease are insidious In *secondary amyloidosis* the clinical picture ordinarily is overshadowed by the inciting disease Amyloid disease of the kidneys is most apt to become clinically apparent with marked albuminuria cylindruria edema hypoalbuminemia and more or less pronounced hypercholesterolemia—in severe cases the full blown nephrotic syndrome Obliteration of glomeruli and subsequently of entire nephrons may become extensive enough to cause hypertension and uremia terminating as a contracted kidney Diffuse involvement of the liver may be suggested by hepatomegaly with a firm blunt smooth nontender liver edge Ascites may occur but jaundice and significant hepatic failure are rare In the author s experience there may be brom

matory cells with more or less fibrous tissue replacement Similar changes may involve fat deposits in addition to those in the subcutaneous layers—for example pancreatic adipose tissue and omental mesenteric peripelvic periadrenal and epicardial deposits Moreover extensive fatty infiltration and central necrosis of the liver with hemorrhage occur apparently quite regularly Fatty and hydropic degeneration of the pancreas and adrenal cortex have been described as have fat emboli in the lungs

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Melanosis and Melanuria

The brown or black pigments called melanins are high molecular polymers of oxidation products of ortho-dihydroxyphenol derivatives They are formed for the most part from tyrosine which is oxidized by tyrosinase to dihydroxyphenylalanine ("dopa") then to a red quinone designated hallachrome which is converted to indole quinones and finally polymerized to form melanins

The melanins are elaborated by melanoblasts normally present in the skin and other organs Abnormal deposition of melanins is called *melanosis* and should be distinguished from darkening of the skin or membranes due to deposition of silver (argyria) bismuth (bismuthia) iron (hemochromatosis hemosiderosis) bile pigments or other substances Darkening of the urine due to excretion of melanin is termed *melanuria*

Increased pigmentation of the skin or mucous membranes need not of itself have any deleterious connotation as for example the tanning or freckling of the skin after exposure to ultraviolet rays or the pigmentation particularly of the face (chloasma gravidarum) commonly accompanying pregnancy Darkening of the skin also occurs after radiation therapy and after prolonged mechanical irritation (scratching due to vermin infestation or to other causes of pruritus) or prolonged administration of certain chemicals notably arsenicals

The chief importance of diffuse or localized melanosis lies in its frequent association with a variety of significant disorders The melanosis of Addison s disease for example may provide an important clue to diagnosis in this disorder the decrease in corticosteroid secretion leads to augmented release of melanocyte stimulating hormones (intermedin) by the pars intermedia of the pituitary gland The blue-black ears of ochronosis are characteristic of that disorder Vitamin deficiencies in pellagra and sprue not infrequently are accompanied by increased pigmentation of the skin particularly of the exposed areas In neurofibromatosis (von Recklinghausen s disease) sharply defined areas of skin pigmentation characteristically are present even if subcutaneous nodules are inconspicuous or absent and are an aid in diagnosis Similar pigmented areas usually more irregular in configuration are apt to develop in involved neurodermal segments in fibrous dysplasia of bone *Familial polyposis of the small intestine* with early neoplastic degeneration is sometimes identifiable by the presence of melanosis of the skin about the mouth and nose with discrete areas of pigmentation of the buccal mucous membranes and on the hands Diffuse melanosis of exposed areas of skin may be observed also in association with porphyria systemic lupus erythematosus dermatomyositis and primary biliary cirrhosis

Melanosis and melanuria occur in association with *malignant melanomas* These tumors usually arise from a pigmented flat hairless mole or from the uveal tract and metastasize widely and rapidly They are apt to elaborate melanin pigments in considerable quantity many however as colorless precursor melanogens In addition to pigmented metastases there may be diffuse melanosis of the skin and other organs In such instances the urine may contain a sufficient quantity of pigment to take on a brown or black color when voided often however the urine turns dark only upon standing because of the oxidation of melanogens Addition of ferric chloride gives a dark brown or black precipitate bromine water forms a yellow precipitate which darkens gradually The dark color of the urine due to the presence of melanins should be readily distinguishable from that of hemoglobinuria porphyrinuria and alkaptonuria by these and other appropriate tests

Acanthosis nigricans is characterized by the appearance of soft velvety brownish to-black verrucous plaques of cutaneous folds characteristically present in the axillae but sometimes also involving the external genitalia perianal area nipples and umbilicus and occasionally affecting the mucous membranes There may be hyperkeratosis of the palms and soles with papillomatous elevations elsewhere often associated with local loss of hair The juvenile form usually present at birth is benign Onset after the age of forty is associated in approximately one half of the cases with malignancy preponderantly of the

sulfalein retention and marked increase in serum alkaline phosphatase apparently due to obstruction of intrahepatic excretory channels The spleen is usually only mod erately enlarged however the diffuse type of splenic involvement results in marked splenomegaly occasionally with rupture Manifestations of Addison s disease if pres ent ordinarily are due to associated tuber culosis which can usually be recognized roentgenographically by local calcification Amyloidosis of the gastrointestinal tract may be associated with chronic diarrhea

Whereas secondary amyloidosis may de velop at any age depending on the under lying disease *primary systemic amyloidosis* occurs usually between the ages of forty and eighty Males are more commonly af fected than females The presenting symp toms are usually those of intractable con gestive heart failure with dyspnea edema and fluid in serous cavities Macroglossia may be striking with dysarthria and dys phagia Asthenia and weight loss are the rule in late stages Deposits in the skin may simulate scleroderma or myxedema Hypertension lymphadenopathy pains in joints and extremities and purpura occur An occasional feature is the carpal tunnel syndrome In some cases the distribution *of amyloid deposit is predominantly in the* liver spleen and kidneys as in secondary amyloidosis with corresponding symptoma tology

In the familial form of primary systemic amyloidosis which is compatible with long life the presenting symptoms are apt to be neuropathies involving the upper and lower extremities Associated with these there may be amyloid deposits in the skin liver and spleen cardiac enlargement and impaired function disturbances in ocular movements and involvement of the gastro intestinal tract

The clinical manifestations of amyloi dosis associated with *multiple myeloma* may be inconspicuous in relation to those of the underlying disorder but occasionally dominate the picture Ordinarily the distri bution of the deposits and the correspond ing symptomatology resemble primary sys temic amyloidosis and are as polymorphic in clinical expression Predominant hepato-*splenomegaly* and amyloidosis of the kid ney may occur

Localized amyloid tumors of the larynx may cause hoarseness and if large may result in obstructive dyspnea They can be visualized by laryngoscopy or bronchoscopy and identified by histological examination of biopsy specimens

Diagnosis Amyloidosis should be kept in mind as a possible complication of the suppurating diseases with which *secondary amyloidosis* is associated Development of marked albuminuria or the nephrotic syn drome in the course of these diseases should raise the question of amyloid nephrosis Needle biopsy *of the liver or kidney may* secure the diagnosis Gingival biopsy is often helpful but does not disclose amyloid deposits in many cases

The Congo red test which depends upon rapid removal of the injected dye from the *blood* as a result of selective adsorption by amyloid deposits is a useful but sometimes uncertain diagnostic method Taran and Eckstein recommend standardization of the procedure by use of 1 ml of a 1 per cent aqueous solution per 10 pounds of body weight Adsorption of at least 90 per cent of the dye in one hour constitutes a positive test and good evidence for diffuse amyloi dosis A smaller percentage of dye is re moved in nonamyloid cases or when the amyloid deposits are small or of a type that does not readily adsorb the dye

Recognition of *primary systemic amyloi dosis* is difficult the cardiac manifestations simulating constrictive pericarditis or ar teriosclerotic heart disease Macroglossia *may suggest the diagnosis* which depends upon biopsy and even then may be uncer tain because of erratic staining properties of the amyloid The Congo red test fre quently is negative or inconclusive for the same reason In the hereditary form a *familial history may suggest the diagnosis*

Prognosis and Treatment The average period of survival from onset of symptoms in nonfamilial *primary systemic amyloido sis* is about three years Death is usually due to intractable cardiac failure Treat ment is symptomatic

In *secondary amyloidosis* therapy is aimed at the underlying suppurative dis order Control of suppuration by treatment with antibiotics has a prophylactic effect on complicating amyloidosis as indicated by a reduction in incidence in recent years

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Melanosis and Melanuria

The brown or black pigments called melanins are high molecular polymers of oxidation products of ortho-dihydroxyphenol derivatives They are formed for the most part from tyrosine which is oxidized by tyrosinase to dihydroxyphenylalanine (dopa) then to a red quinone designated hallachrome which is converted to indole quinones and finally polymerized to form melanins

The melanins are elaborated by melanoblasts normally present in the skin and other organs Abnormal deposition of melanins is called *melanosis* and should be distinguished from darkening of the skin or membranes due to deposition of silver (argyria) bismuth (bismuthia) iron (hemochromatosis hemosiderosis) bile pigments or other substances Darkening of the urine due to excretion of melanin is termed *melanuria*

Increased pigmentation of the skin or mucous membranes need not of itself have any deleterious connotation as for example the tanning or freckling of the skin after exposure to ultraviolet rays or the pigmentation particularly of the face (chloasma gravidarum) commonly accompanying pregnancy Darkening of the skin also occurs after radiation therapy and after prolonged mechanical irritation (scratching due to vermin infestation or to other causes of pruritus) or prolonged administration of certain chemicals notably arsenicals

The chief importance of diffuse or localized melanosis lies in its frequent association with a variety of significant disorders The melanosis of Addison s disease for example may provide an important clue to diagnosis in this disorder the decrease in corticosteroid secretion leads to augmented release of melanocyte stimulating hormones (intermedin) by the pars intermedia of the pituitary gland The blue black ears of ochronosis are characteristic of that disorder Vitamin deficiencies in pellagra and sprue not infrequently are accompanied by increased pigmentation of the skin particularly of the exposed areas In neurofibromatosis (von Recklinghausen s disease) sharply defined areas of skin pigmentation characteristically are present even if subcutaneous nodules are inconspicuous or absent and are an aid in diagnosis Similar pigmented areas usually more irregular in configuration are apt to develop in involved neurodermal segments in fibrous dysplasia of bone *Familial polyposis of the small intestine* with early neoplastic degeneration is sometimes identifiable by the presence of melanosis of the skin about the mouth and nose with discrete areas of pigmentation of the buccal mucous membranes and on the hands Diffuse melanosis of exposed areas of skin may be observed also in association with porphyria systemic lupus erythematosus dermatomyositis and primary biliary cirrhosis

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stomach but also arising from the uterus liver rectum large bowel ovary breast and bronchi These tumors are usually adenocarcinomas and highly malignant The significance of this association is not known

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Hemochromatosis

Definition Hemochromatosis (iron storage disease) is a chronic disease characterized by the deposition of iron in body tissues with eventual fibrosis and functional insufficiency of those organs severely involved Depending on the manner in which excess iron deposits are produced hemochromatosis may be characterized as idiopathic dietary or due to blood transfusion

Morbid Anatomy At autopsy the unique finding in hemochromatosis is a bronze pigmentation of body tissues due to widespread deposition of hemosiderin These iron deposits are heaviest in the liver but are also prominent in the reticuloendothelial tissue endocrine glands striated muscle and skin The liver is sclerotic and usually large (average weight 2400 gm) Fibrosis of the pancreas and of lymph nodes containing large amounts of iron is commonly though not invariably found Iron deposits within the heart muscle cells are of particular significance because of the associated cardiac dysfunction

Pathogenesis and Pathologic Physiology Recently many of the unusual features of idiopathic hemochromatosis have been clarified through isotopic studies of iron metabolism Excretion of iron in man has been shown to be negligible absorption rather than excretion controls the amount of body iron When tissue iron stores are adequate a mucosal block prevents excessive iron absorption In idiopathic hemochromatosis this is for unknown reasons ineffective and a great surplus of iron accumulates Because the iron accretion is gradual symptoms do not usually appear until the patients are beyond thirty five years of age (70 per cent between the ages of forty to sixty years) The predominance of hemochromatosis in the male (about 95 per cent) is understandable when one considers the difference in iron balance between the two sexes The male is unable to rid himself of iron once it is absorbed but the female does so continually through menstruation and pregnancy

Tissue iron in idiopathic hemocromatosis represents iron absorbed and stored in a form available for hemoglobin formation rather than a product of abnormal tissue metabolism The liver is the shock organ for such storage and may contain up to 50 gm of iron in the form of ferritin and hemosiderin As the storage capacity of the liver is exceeded iron spills over into other receptor tissues particularly into the endocrine glands and skin The serum iron becomes elevated and saturates the iron binding protein of the serum which transports it Liver fibrosis is thought to be produced by the large amounts of iron which accumulate in the periportal areas of the liver lobule The defect in absorption is not limited to iron since other metals may be found in excess in the tissues Alcoholism and dietary deficiency do not figure as essential factors in this disease as they do in Laennec s cirrhosis although a history of excessive alcohol intake has been noted in roughly one third of the patients with idiopathic hemochromatosis Enough data are available to indicate a significant familial and hereditary tendency Idiopathic hemochromatosis must be considered a rare disease although it undoubtedly occurs more frequently than the reported autopsy incidence of 0 003 to 0 08 per cent

It is increasingly apparent that *transfusion hemochromatosis* may be pathologically indistinguishable from the idiopathic type and may also present evidence of damage to the liver heart and pancreatic islets Since initial deposition if iron from transfused red cells is in the reticuloendothelial system there continues to be discussion of histological differences in iron distribution between these two types of iron storage disease Time and perhaps other factors such as the level of erythropoietic activity may play a role in redistribution of iron It is considered that in excess of 100 transfusions represents a potentially harmful iron load

Patients with what may be designated *dietary hemochromatosis* have been reported by Gillman and his co workers Here

a high dietary intake of iron is maintained over many years and again the pathological appearance of the liver may be similar to that seen in idiopathic hemochromatosis although other nutritional deficiencies probably play an important role in tissue damage The prolonged oral administration of medicinal iron to the anemic patient has also been reported to lead to hemochromatosis Recent studies suggest that the anemic patient with a hyperplastic erythroid marrow is more likely to absorb excessive amounts of medicinal iron than the patient with an acellular marrow

Clinical Picture The presenting complaints in idiopathic hemochromatosis may relate to skin pigmentation diabetes hepatomegaly symptoms of severe liver disease endocrine dysfunction and heart failure

Pigmentation of the skin is of two types In about half of the patients there is an Addisonian like bronzing due to increased melanin In the remaining patients the skin acquires a blue gray or leaden cast as a result of iron deposition The pigment is distributed most prominently over the genitalia face and arms and in skin folds Mucous membranes are involved in only about 15 per cent of the patients

The liver is usually palpable and the spleen is also palpable in about half the cases The enlarged liver is frequently associated with upper abdominal pain which may occasionally be excruciating and knife like simulating biliary colic or perforated peptic ulcer Visible jaundice is unusual There is frequently no indication of the severe liver disease other than general body wasting Many patients as a result of some acute illness or stress situation suffer acute liver decompensation with coma and death rapidly supervening Hepatoma is an important complication in the older patient Hemorrhage from a ruptured esophageal varix is less frequently encountered than it is in nonpigmentary cirrhosis and evidence of increased collateral circulation is rare Ascites may appear as a terminal event Sexual impotence is a common complaint in the late phase of the disease but may occur when the patient is otherwise asymptomatic Testicular atrophy loss of axillary and chest hair and occasional gynecomastia may be regarded as related to liver dysfunction

The diabetes of hemochromatosis is mild at the onset but progressively worsens A few patients are sensitive to insulin but a greater number are relatively resistant occasionally requiring several hundred units a day

Cardiac deposits of hemosiderin are frequently associated with arrhythmias and congestive heart failure which responds poorly to conventional therapy A moderate macrocytic anemia is found only in the late stage of the disease In the early phases the hemoglobin concentration is apt to be above normal

Diagnosis There is little difficulty in recognizing this disease in a patient with the classic tetrad of skin pigmentation liver disease diabetes and cardiac failure A high index of suspicion in the presence of any two of these four cardinal findings will frequently lead to the diagnosis Laboratory studies center around the demonstration *first* of excessive iron stores and *second* of hepatic pancreatic or cardiac disease When liver disease is suspected a needle biopsy is the most conclusive diagnostic procedure but its use is restricted because of the risk involved (In this type of liver disease abdominal exploration and direct biopsy are even more hazardous) An elevated serum iron and saturation of the iron binding capacity of the serum are the most useful special laboratory findings in the demonstration of iron excess Other tests employed in order of their usefulness are examination of urinary sediment examination of the sternal marrow for hemosiderin skin biopsy and biopsy of gastric mucosa Iron in the skin is of diagnostic significance when found in the epithelial cells of the sweat glands

Prognosis and Treatment The average duration of life after diagnosis has been lengthened from the eighteen months reported by Sheldon in 1935 Since the advent of insulin diabetes has been adequately controlled in the majority of cases In patients under forty most fatalities are ascribable to cardiac failure in those between the ages of forty and sixty hepatic failure and infection may cause death and in patients over sixty a hepatoma may develop

Supportive therapy in idiopathic hemochromatosis is directed at management of the liver disease and when it is present diabetes A high caloric diet (50 calories per kg) and supplementary B vitamins appear to be beneficial Insulin should be prescribed as required with this diet It would seem wiser in view of the liver disease to allow some glycosuria rather than risk hypoglycemia

On the assumption that iron deposits are chiefly responsible for tissue damage specific therapy should be directed toward removal of iron through phlebotomy In pa

tients with idiopathic hemochromatosis weekly phlebotomies of 500 ml are well tolerated Each phlebotomy removes 200 to 250 mg of iron from the blood which is replaced by an equivalent amount of iron from the tissue stores In contrast to normal persons who rapidly become anemic on this regimen patients with idiopathic hemochromatosis maintain their red cell hematocrits at levels between 35 to 45 per cent Over a period of two to three years the bulk of the iron deposits in the tissues will be mobilized for hemoglobin production and removed by bleedings

The reversibility of hemochromatosis will depend on the amount of tissue damage present before the therapy is undertaken and the extent to which the iron *per se* is responsible for tissue damage Experience with this form of treatment is sufficiently encouraging to indicate its routine usage but as yet is too limited to permit evaluation of its long term effect on the course of the disease

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Agammaglobulinemia

Definition This is a syndrome characterized by marked deficiency of plasma gamma globulins impairment of antibody formation and frequent severe infections

Etiology and Pathogenesis The hypogammaglobulinemias may be divided into two main groups on the basis of their pathogenetic mechanism (Table 1) In the *primary* group comprising the true agammaglobulinemias or antibody deficiency syndromes the deficiency is due to a diminished rate of synthesis This is associated with morphological changes in the lymphoid tissues and failure of plasma cells to develop in the lymphoid follicles and bone marrow and of antibodies to appear in the blood after antigenic stimulation This alteration in structure and function of the lymphoid system may have various causes In the *secondary* group hypogammaglobulinemia is due to loss of gamma globulins from the body or their increased catabolism while synthesis remains relatively normal in this group other proteins such as albumin are affected antibody formation may occur and infection is less of a problem except in the nephrotic syndrome

Symptoms and Signs The outstanding clinical manifestations are recurrent severe infections usually due to the common pyogenic bacteria These differ from infections in normal persons only by their frequency and seriousness Upper respiratory tract infections with sinusitis conjunctivitis otitis media and repeated episodes of pneumonia are particularly common furunculosis bacteremia meningitis septic arthritis and gastrointestinal disorders with a spruelike picture in the adult may also occur

Tonsils adenoids thymus and lymph nodes are small in congenital cases but tender regional lymphadenopathy may develop with infection Some acquired cases have similar findings whereas in others persistent lymphadenopathy and splenomegaly may be noted

Viral infections seem to be tolerated more normally although fatal hepatitis presumably of the homologous serum type has been reported twice

Complications are of two types (1) *suppurative* with local injury from infection bronchiectasis being most frequent and (2) *nonsuppurative* including chronic arthritis observed in about one third of congenital cases and rarely dermatomyositis or scleroderma

Laboratory Findings Those associated with acute infections are not unusual except that neutropenia or hyperleukocytosis are frequently observed The agammaglobulinemic state may be recognized by study of the serum which usually reveals (*a*) as presumptive evidence (1) low globulin concentration associated with normal albumin (2) absent or very low isohemagglutinin titer (3) low zinc turbidity value (4) absence of specific antibodies expected from previous infections or immunizations (*b*) as diagnostic evidence (1) virtual absence of gamma globulins on electrophoretic analysis (2) gamma globulin level below 150 mg per 100 ml by more accurate immunological methods

Treatment Acute infections require intensive antimicrobial chemotherapy which should be continued until all signs of infection have disappeared In the absence of bronchiectasis or other structural changes from preceding infections replacement therapy with human gamma globulin is quite effective in prevention of severe infections The aim is to keep the gamma globulin level above 150 mg per 100 ml This requires an initial dose of 0 2 gm per kg (0 6 ml per pound) and a maintenance

Table 1 Hypogammaglobulinemia

TYPE	ETIOLOGY	MECHANISM	PATHOLOGY OF LYMPHOID TISSUE	PLASMA GAMMA GLOBULINS Normal 700-1200 mg per 100 ml
PRIMARY (AGAMMAGLOBULINEMIA)				
1 *Transient* Infants (both sexes) 1-5 months	Immaturity of lymphoid tissues		Immature follicular structure Few plasma cells	(mg per 100 ml) <150
2 *Congenital* (Chiefly males) 4 months and older	Genetic (Sex linked recessive)	Decreased Synthesis	Poor follicular structure Absence of plasma cells	0-25
3 *Acquired* (Both sexes) Any age	a Destruction or replacement of normal lymphoid *tissues* b Idiopathic		a Granulomatous or neoplastic infiltration of *lymphoid tissues* Few plasma cells b Variable (hyperplastic or hypoplastic) follicular structure Very few plasma cells	0-100
SECONDARY (HYPOGAMMAGLOBULINEMIA)				
1 *Idiopathic Hypoproteinemia*	Not known	Increased catabolism	Normal	200-400
2 *Nephrotic Syndrome*	Not known	a Increased catabolism b Loss *in urine*	Normal	200-300

dose of 0 1 gm per kg (0 3 ml per pound) given in single or divided doses every four weeks

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Dehydration and Fluid Balance Physiological Principles

The term dehydration as used in clinical medicine refers to a condition in which the volume of body fluids and particularly the volume of extracellular fluid is diminished Because of the multiplicity of derangements which may contribute to dehydration and the varying severity and chemical nature of the disturbance each patient constitutes an individual problem in evaluation and therapy Therefore it is important that the *principles* involved in fluid and electrolyte balance be clearly understood

The volume and the total concentration of dissolved substances in body fluid are the dimensions particularly pertinent to this consideration of fluid and electrolyte balance The maintenance of composition with respect to specific electrolytes and the regulation of acid base equilibrium while of vital importance and not infrequently disturbed in association with dehydration is beyond the scope of the present discussion

Normal Anatomy Water constitutes some 55 to 60 per cent of the weight of an average normal person but varies in amount inversely with the body s fat content The plasma and the interstitial fluid of tissues which together *constitute the extracellular* fluid comprise slightly more than one third of the body water the remainder is within cells The cell membranes may be regarded as freely permeable to water but do not allow the *free* passage of strong electrolytes

Water moves into and out of cells in response to changes in osmotic activity across the cell membranes Water added to the extracellular compartment is rapidly distributed in the total body water Conversely if solute to which cell membranes are impermeable is added to the extracellular fluid water is withdrawn from cells In each case the total concentration is ultimately uniform throughout body water

Extracellular fluid throughout the body is a phase of fairly uniform composition in which sodium ions and their complement of anions chiefly chloride and bicarbonate constitute all but a small fraction of the solute Intracellular fluid varies somewhat from tissue to tissue but in general contains little sodium and chloride The major cation potassium is balanced probably largely by organic phosphates and the anionic groups of proteins The disparity in electrolyte distribution across cell membranes is maintained by the metabolic activity of the cells

Measurement of the Volume of Body Fluid and Its Compartments Numerous procedures for the estimation of the volume of body water extracellular fluid and plasma have been devised For the most part these are clearly designed for investigative purposes and have little utility in the study and treatment of the individual patient However since certain generalizations concerning the behavior of body fluid compartments have been derived from studies using these techniques it is well to be informed concerning their nature and limitations and the reservations necessary in their interpretation

The estimation of *total body water* is usually based on the dilution principle Satisfactory approximations can be made by determining the volume in which heavy water or antipyrine is distributed Sufficient time must be allowed for complete distribution of the substance in body water and in the case of antipyrine to obtain an estimate of the rate of metabolic breakdown of the drug

The volume of *extracellular fluid* has been estimated as the apparent volume of distribution of a number of substances among which are thiocyanate chloride bromide thiosulfate sulfate (labeled with S^{3}) inulin mannitol and sucrose None of these substances can be considered to yield quantitatively reliable values for various reasons including failure to remain in an exclusive extracellular position rapid excretion so that prolonged intravenous infusion under completely stable conditions is necessary during their equilibration in extracellular fluid and failure to become evenly distributed in extracellular fluid within a time which can reasonably be devoted to the procedure Since *intracellular fluid* is evaluated as the difference between total and extracellular volumes the estimate is subject to summation and magnification of the errors of the two individual determinations

The evaluation of *plasma volume* by dilution methods is subject to variable errors due to losses of dye (or tagged albumin) from the circulating blood while estimates based on the use of tagged red cells require assumptions concerning the proportion of red cells to plasma in the body as a whole a ratio not necessarily given by the hematocrit determined in peripheral blood

Normal Fluid and Electrolyte Balance and Its Regulation The body normally gains fluid and electrolytes from the exterior only through the gastrointestinal tract Water is derived from the intake of liquids and from the food both as preformed water and that obtained upon oxidation of the foodstuffs Those electrolytes which are of major concern in fluid balance—sodium potassium and chloride ions—are present as such in the food

Fluid and electrolyte or both are lost to the environment through the lungs and skin and in the feces and urine Air is inhaled at the ambient temperature and humidity and is exhaled saturated with water vapor at body temperature Losses of water through the lungs are therefore increased by increased pulmonary ventilation and when the water content of the inspired air is low No electrolyte is lost by this route

Output of water through the skin in the form of evaporation or as visible sweat may vary in amount over a wide range The salt content of sweat is appreciably lower than that of extracellular fluid and is subject to some physiological regulation being reduced when there is a stimulus for retention of salt in the body In the absence of visible sweating electrolyte loss through the skin is negligible

Although up to 10 liters of isotonic fluid are secreted into the gastrointestinal tract each day practically all of this water and electrolyte in addition to that ingested is normally reabsorbed into the body The feces normally contain only a minimum of water sodium potassium and chloride

Since losses through lung and skin are dependent on environment and the func

tions of respiration and temperature regu lation respectively and excretion in the stools is normally negligible only the kid ney can modify the output of salt and water in a manner directly subservient to the regulation of the volume and concentra tion of body fluids In general the con centration of body fluids is regulated by the retention or excretion of water whereas volume is regulated by the retention or excretion of salt

Regulation of body fluid concentration is initiated in the hypothalamus where re ceptors responsive to changes in the effec tive osmotic pressure of body fluid regulate the release of antidiuretic hormone from the neurohypophysis Secretion is increased when osmotic pressure is high diminished when osmotic pressure is low Antidiuretic hormone in turn increases the reabsorp tion of water by the renal tubules pre venting the excretion of a dilute urine and facilitating the formation of urine hyper tonic to plasma The water thus conserved dilutes the body fluid reducing osmotic pressure Since sodium salts contribute some 85 per cent of the total solute of extracellular fluid the plasma sodium con centration is an excellent indicator of the effective osmotic pressure of the body fluids except when a high concentration of some other solute to which cells are relatively impermeable (*e g* glucose) is present Urea does not contribute to *effective* os motic pressure since it permeates cells easily

Regulation of the volume of extracellular fluid is accomplished by modification of the excretion of sodium and the anion which accompanies it The chain of events in this homeostatic process is not clearly under stood Several contributory factors are rec ognized including changes in the rate of glomerular filtration and variation in the secretion of adrenal steroids which regulate sodium reabsorption by the renal tubules other factors are probably also involved Normally losses or gains of sodium are not accompanied by appreciable changes in the sodium concentration of extracellular fluid since operation of the hypothalamic regu lators of water loss accurately maintains the total effective osmotic activity and hence the plasma sodium concentration at normal levels Changes in sodium balance are therefore manifested largely as changes in extracellular fluid volume and short of actual measurements of balance are detected as changes in weight and by the clinical signs of changes in extracellu lar fluid volume

Regulation of the volume of intracellular fluid is poorly understood Most variations are probably associated with (1) changes in the organic components of cells and (2) dilution and concentration of cell solutes as a result of accession of water to or loss of water from the body

Exchanges of Fluid and Electrolyte Be tween Intra and Extracellular Spaces In recent years data have been presented which have been interpreted to indicate that under the influence of certain stresses or the administration of adrenocortical hor mones there may be transfers of fluid and electrolyte from the intracellular space into the extracellular fluid which are not de pendent upon exchanges with the exterior or changes in the osmotic pressure of body fluids For the most part these conclusions are based on the estimation of body fluid compartments and therefore subject to reservations on the basis of methodology It is undoubtedly true that sodium can replace an appreciable fraction of the intra cellular potassium when the body has been depleted of the latter and that the sodium is extruded when potassium is again avail able It is also probable that bone can serve as a source of cation in the presence of acidosis of the extracellular fluid (and therefore can presumably accept addi tional cation in alkalosis) Except for these considerations it is best to regard exchanges of fluid and electrolyte between compart ments of the body water as determined by the organic constituents within cells the movement of water in response to changes in total solute in one compartment or the other and the capacity of cells to main tain with the potassium available the nor mal gradients of sodium and potassium across cell membranes

Pathological Physiology The level of in take required to maintain fluid and electro lyte balance varies widely The *minimum* intake of water under normal conditions is that required to replace losses through lung and skin and to put out in a urine of maximum concentration those solutes which must be excreted In persons with free access to water the thirst mechanism is adequate to insure sufficient intake for maintenance of the normal concentration of body fluids In the absence of abnormal output small amounts of sodium and potas sium are adequate to maintain balance and are obtained from any but the most re stricted of dietary intakes The presence of abnormal losses may of course greatly increase intake requirements

Loss Increases in output by any of the

normal routes as well as from the development of abnormal routes may lead to deficits of fluid and electrolyte While generally of minor importance relative to the other disturbances it accompanies the loss of water by *evaporation* in hyperventilation is a factor which should not be neglected The considerable losses of both water and salt which occur with profuse sweating are frequently of clinical consequence while leakage of extracellular fluid through areas denuded of skin as by burns may lead to grave disturbances of fluid balance

The *gastrointestinal tract* is a potential source of difficulty in the maintenance of fluid balance since it is the route of normal replacement and since a large fraction of the body s extracellular fluid is secreted into and reabsorbed from it each day Large losses of such fluid may occur with either diarrhea or vomiting the latter being complicated in that it may cut off intake The development of fistulous connections between the gastrointestinal tract liver or pancreas and the exterior commonly leads to very large deficits of fluid and electrolyte if adequate replacement is not undertaken

Regulation is ultimately dependent upon *renal function* and since this function with respect to fluid and electrolytes represents the integration of a number of processes each with its intrinsic mechanism and extrarenal regulator it is subject to a number of disturbances each of which may arise from either local or nonrenal causes The initial process in urine formation *glomerular filtration* is dependent upon the anatomical and functional integrity of the glomeruli and upon the blood pressure The energy is thus contributed by the heart The restriction of glomerular filtration in the face of a falling cardiac output in dehydration and shock is often quite out of proportion to the fall in blood pressure since compensatory vasoconstriction is often far more marked in the kidney than in the body as a whole Although such reductions of glomerular filtration tend to minimize fluid output when fluid is badly needed they seriously impair the capacity to maintain the composition of body fluids and when renal vasoconstriction has been severe and prolonged function may not be restored when shock has been alleviated

Abnormalities of water excretion leading to dehydration with increased osmotic pressure or overhydration with decreased total solute concentration result from failure of the renal tubules to reabsorb water to form a hypertonic urine or to reject water in a dilute urine The capacity to form a concentrated urine is vulnerable to many insults and is often the first function to be impaired in such disorders as nephritis and hypertensive disease and one of the last to be restored following acute renal damage produced by shock or nephrotoxic agents Far less commonly the excretion of a dilute urine is the result of a lesion in the hypothalamic hypophyseal system leading to diabetes insipidus Whatever its cause *incapacity of the kidney to form a concentrated urine* is a common source of fluid imbalance since any interruption of intake such as may be produced by vomiting is likely to lead to rapidly developing dehydration with further impairment of renal function

Although inability to form a concentrated urine is usually due to organic renal disease *failure to excrete a dilute urine* when body fluids are diluted is preponderantly attributable to functional nonrenal disturbances The intrinsic capacity to form a dilute urine is often maintained after organic renal disease has led to severe limitation of concentration However increased secretion of antidiuretic hormone which prevents the formation of a dilute urine may be produced by stimuli other than the normal one of a rise in the osmotic pressure of body fluids Among such stimuli are a number of drugs (*e g* nicotine morphine barbiturates) emotional disturbances and operative trauma Failure to excrete water normally is discussed more fully in the section on Hyponatremia

Impairment of the ability of the renal tubules to reabsorb sodium is occasionally a very striking feature of renal disease (so called salt losing nephritis) but it is best to consider some *limitation of the capacity to limit loss of sodium* when intake is severely restricted as an almost constant concomitant of advanced disease of the kidney Less commonly the tubules fail to reabsorb sodium because of failure of normal hormonal regulation (adrenal insufficiency) The loss of sodium leads to contraction of extracellular fluid volume which in turn may lead to impairment of water excretion and a fall in the sodium (total solute) concentration of extracellular fluid

Abnormal losses of sodium with depletion of extracellular volume may also occur even though the sodium transport mechanism and its regulation are fundamentally normal when there is *massive excretion of solute* (*e g* glucose in uncontrolled diabetes) which by osmotic effect carries out increased amounts of electrolyte This effect

is greatly increased when the solute excreted is anion for instance the keto acid of diabetic acidosis or the chloride from ingested ammonium chloride since this must be balanced by the equivalent amount of cation The tendency of such excretory loads to produce rapid sodium depletion is greatly magnified in the presence of renal damage with limited ability to reabsorb sodium and to form ammonia with which to replace it in the urine

Clinical Manifestations The clinical manifestations of loss of fluid and electrolyte are more or less independent of the nature of the defect which produces them and in general are those of diminished extracellular fluid and circulating blood volume—weakness anorexia nausea and vomiting circulatory insufficiency with failing renal function and ultimately shock and coma When loss of water predominates over that of solute and osmotic pressure rises thirst is particularly prominent although to a lesser extent a fall in volume alone may produce an increased desire for water

Diagnosis An exploration of the patient s *history* as to intake and output of fluid has much to contribute to the diagnosis of disorders of fluid balance and to the selection of appropriate therapy Such an evaluation should include consideration of both the volume and the probable electrolyte content of fluids gained or lost by all of the normal and abnormal routes Often the presumptive diagnosis of dehydration can be made and proper therapeutic measures undertaken from such consideration alone

On *physical examination* the findings are largely those of diminished extracellular fluid volume weakness and lassitude thirst and dryness of the mouth (these particularly marked when body fluid concentration is increased) loss of skin elasticity a sunken appearance of the eyeballs weakness of the pulse and hypotension In severe grades of volume loss the signs of circulatory failure may advance to frank shock which may be accompanied by stupor or coma and severe oliguria or anuria

Laboratory Findings Changes in the effective concentration of body fluids are best evaluated by measurement of the plasma sodium concentration Consideration must be given however to the concentration of other substances particularly glucose that may constitute an appreciable fraction of that solute which does not easily penetrate cells When a flame photometer is not available for estimation of sodium and there is no reason to suspect the presence of increased amounts of anions other than chloride and bicarbonate in the blood (as in ketosis or advanced renal insufficiency) determination of the plasma chloride and carbon dioxide content may give a useful approximation of the plasma sodium The latter is about 10 mEq per liter higher than the sum of chloride and bicarbonate when both are expressed in mEq per liter

There are no wholly satisfactory laboratory methods for estimating the volume of extracellular fluid Since changes in blood volume are frequently responsible for the severe clinical manifestations of loss of extracellular volume a rough approximation of changes in plasma volume such as can be obtained from the hematocrit and from the plasma protein concentration may be useful Only when changes from the normal are large (and usually only when the values are increased) can any weight be given to these determinations in evaluating the initial status of the patient Thereafter short term changes in plasma volume can be followed but it should be kept in mind that a rise in plasma protein means a decrease in the fluid of plasma only if the total circulating plasma protein has not increased Similar consideration is necessary with respect to the hematocrit and circulating red cell mass

The level of urea or nonprotein nitrogen in the blood is useful in following the effects of dehydration on renal function Considerable elevation of these levels may result from dehydration even if the kidneys are intrinsically normal However the level of urea in the blood is dependent upon the rate of protein catabolism as well as on the function of the kidneys

Treatment Unfortunately dehydration of clinical significance is not infrequently permitted to develop in persons under medical care because attention is devoted to the underlying problem and fluid and electrolyte balance neglected or because an adequate volume of fluid is administered but the electrolyte content is inadequate The prevention of such disorders of fluid balance may require only nursing attention to keep up fluid intake or the addition of salt to ingested fluid or food when loss of sodium is high When losses are too large to be compensated by oral intake or when gastrointestinal disorders render oral administration impracticable parenteral fluid therapy may be required The regulatory capacity of the kidneys makes it easier to maintain

normal fluid balance than to correct it when depletion has progressed to impairment of renal function

When dehydration is an established problem the primary objective should be the prompt relief of circulatory insufficiency if this is part of the clinical picture Simultaneously restitution of a normal volume and concentration of the body fluids along with correction of other complicating disturbances such as acidosis or alkalosis should be pressed as rapidly as is compatible with safety The possibility of relieving the disorder responsible for precipitating the dehydration should not be overlooked although delay until the more serious aspects of the dehydration have been controlled may be necessary Milder dehydration without impairment of the circulation can often be treated by increasing the intake of fluid (to perhaps 3 liters per day) and sodium chloride (to possibly 10 gm per day) by mouth

The management of fluid balance by the parenteral administration of fluids should be guided by consideration of the volume and composition of the deficits in each of the divisions of the body fluid In the presence of reasonably normal renal function some reliance can be placed upon the kidneys capacity to retain selectively those components needed while discarding others —provided that *all* of the necessary materials are supplied in sufficient quantities that the circulation is adequate for effective operation of the kidney and provided that there is not present some powerful stimulus to retain some specific body fluid component Excesses of water or sodium for example are often retained presumably because of overactivity respectively of the hypothalamic hypophysial system and adrenal cortex in severely ill patients or those who have recently undergone surgery despite the fact that such retention may distort volume and concentration of body fluids

The aspect of dehydration most threatening to the well being or even the survival of the patient is the diminution in blood volume Restitution is most rapidly accomplished by the administration of whole blood and this is the treatment of choice in *severe dehydration* in which shock is present or threatening While preparation for transfusion is in progress treatment should be initiated with the administration of 1 to 2 liters of isotonic sodium chloride solution If whole blood is not available plasma or human serum albumin (diluted with isotonic saline to contain 5 to 7 per cent protein) may be used as a substitute and they are especially indicated when there has been extensive exudation However the danger of hepatitis from pooled human plasma is to be weighed against the expected benefits

Milder abnormalities of volume concentration and acid base balance can be controlled entirely by the administration of isotonic saline solution leaving to selective renal activity the correction of minor deviations in these dimensions When the deviations are more severe more direct measures may be desirable When *losses of water in excess of solute* have resulted in marked increases in concentrations 5 per cent glucose solution will serve as a source of water since the glucose is rapidly metabolized In some patients a marked *decrease of body fluid concentration* may be encountered most often because losses of isotonic fluid have been inappropriately replaced with water or 5 per cent glucose In such instances there may be a place for hypertonic (2 per cent or 3 per cent) sodium chloride solutions since the hypertonic fluids are considerably more efficient in restoring concentrations than is isotonic saline However a low osmotic pressure (plasma sodium concentration) is often found in association with *increased* extracellular volume in cardiac failure cirrhosis and advanced renal failure and the use of hypertonic saline solutions in these conditions is more detrimental than helpful The pathogenesis and treatment of these abnormalities are discussed more fully in the section on Hyponatremia

In dehydration with severe *acidosis* restoration of acid base balance may be hastened if isotonic (one sixth molar) sodium lactate solution is used in place of sodium chloride since oxidation of the lactate make the sodium available as bicarbonate without interposition of renal activity *Alkalosis* is sometimes treated by the intravenous administration of ammonium chloride but the practice is to be discouraged as dangerous and rarely necessary Ammonium ion absorbed from the gastrointestinal tract is fixed as urea in the liver but administered intravenously it is distributed in the general circulation and may have marked toxic effects on the central nervous system The possibility that potassium depletion may in part be responsible for alkalosis should be kept in mind

The addition of potassium chloride to solutions for intravenous use has become common practice for the treatment of *potassium depletion* This may under selected circumstances e g diabetic acidosis metabolic alkalosis be highly beneficial but

the dangers should be recognized and promiscuous use discouraged For further details see the section on Hypokalemia

Certain *precautions* to be taken in the intravenous administration of saline solutions are especially important in the treatment of patients who have or who are likely to develop cardiac insufficiency The too rapid administration of fluids in such patients may precipitate pulmonary edema Keeping infusion rates low periodic examination of the lung bases for rales and frequent determination of the venous pressure may minimize the danger In such persons there may be occasion for subcutaneous administration of saline but poor absorption may be anticipated in the presence of peripheral circulatory failure Another occasion for caution is in the treatment of patients with renal insufficiency in which renal function cannot compensate for miscalculation of fluid requirements This is particularly the case when renal shutdown is complete even though this may have resulted from dehydration and shock If when blood pressure has been restored and the peripheral circulation is adequate a flow of urine has not been established the further administration of fluids will not "force open" the kidneys and indeed attempts to do so may be fatal Conservative expectant treatment with fluid and electrolyte intake carefully balanced to output is required

Specific consideration of the management of dehydration and disturbances in fluid balance is discussed under diseases in which these problems are of major importance *e g* diabetes mellitus adrenal insufficiency uremia etc For normal values of blood constituents see tables at the end of this book

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Hyponatremia

Interpretation The finding of a plasma sodium concentration below the normal range is with a single exception to be mentioned an indication of a reduced effective osmotic pressure of the body fluids It is thus a clear indication of dilution of the body fluids of an excess of water *relative* to the amount of solute Since such dilution of the body fluids is normally the stimulus for the excretion of the excess water in a dilute urine hyponatremia is always a sign of inadequate water excretion *The plasma sodium concentration alone gives no information relevant to the question of whether the body has an excess or a deficit of sodium* The latter can be estimated only from the *volume* of and concentration of sodium in the extracellular fluid and since volume changes are likely to be relatively larger than the changes in sodium concentration extracellular fluid volume is the dominant factor in determining the body sodium content

(The exception to the equivalence of hyponatremia and low effective osmotic pressure is the relatively unusual situation in which a very high concentration of some solute such as glucose which does not readily penetrate cells is present in the extracellular fluid By drawing water from cells or by keeping administered water in an extracellular position such solute may dilute the plasma sodium while total effective osmotic pressure is normal or even high)

Physiology Since impaired water excretion underlies hyponatremia we may approach its causes by a brief review of those factors which contribute to normal water excretion The excretion of dilute urine implies separation of solute and water In the kidney this is accomplished in the distal portions of the renal tubule by the removal of sodium salts from the previously isotonic fluid leaving the excess of water behind to be excreted in the urine Three conditions must therefore be met in order that a dilute urine be excreted (1) An adequate volume of fluid must reach the segment of the tubule in which the dilution occurs (2) this segment must retain the capacity to reabsorb sodium salts and (3) the segment in which the dilution occurs and those distal to it must maintain a low permeability to water so that the excess water cannot diffuse out of the tubule in response to the osmotic gradient which has been created In order that these conditions be met (1) the rate of glomerular filtration must be maintained and an appreciable proportion of the sodium escape reabsorption in the proximal tubule in which no dilution occurs (2) the sodium reabsorption mechanism must perform adequately (3) pituitary antidiuretic hormone must be absent since the specific effect of this hormone is to increase the permeability of the distal portions of the renal tubule to water

Although the subject has not been fully explored it is probable that any or all of these factors may at times contribute to failure of normal water excretion and hyponatremia

Pathogenesis and Treatment In considering some of the more common conditions in which hyponatremia is encountered it is convenient to divide them into those in which hyponatremia is associated with a diminished volume of extracellular fluid and those in which the extracellular volume is expanded

Hyponatremia with Decreased Extracellular Fluid Volume The occurrence of hyponatremia with diminished extracellular fluid volume is almost always the result of losses of body fluids with high electrolyte concentrations *and their replacement with* electrolyte free solutions This may occur in any situation in which dehydration is encountered—profuse sweating losses of gastrointestinal contents by vomiting or diarrhea fistulous drainage etc The dilution may occur because the patient replaces these losses of fluid by drinking water or often in hospital practice because the losses are replaced with electrolyte free fluid in the form of 5 per cent glucose solution In adrenal insufficiency and in renal insufficiency with inability to reduce salt excretion to low levels the electrolyte loss is in the urine In all of these circumstances the primary event is loss of sodium from the body This is responsible for the reduction of extracellular fluid volume The low sodium *concentration* however is the result of failure of water excretion which in turn is due to various combinations of reduced glomerular filtration changes in sodium reabsorption and not infrequently the secretion of antidiuretic hormone in response to stimuli other than the normal one of increased effective osmotic pressure of the body fluids

It is important to recognize that a low plasma sodium concentration indicates a low effective osmotic pressure not only of the extracellular fluid but of the intracellular fluid as well since these osmotic pressures are the same Furthermore since the electrolyte losses which have produced decreased extracellular volumes are generally derived largely from the extracellular compartment the diminished intracellular osmotic pressure is usually the result of the movement of water into cells Thus the intracellular fluid volume is high and the cells expanded in the presence of the shrunken extracellular fluid This underlies the chief danger of hyponatremia—the occurrence of water intoxication Aside from the possibility or frank presence of water intoxication hyponatremia is to be considered a sign of inadequate handling of fluid and electrolyte balance and not a disorder requiring treatment in its own right

Treatment should be aimed at the restoration of a normal total sodium content in the extracellular fluid Under most conditions adequate water excretion is restored when the volume of extracellular fluid is returned to normal so that isotonic chloride solutions can be used for replacement (see section on Dehydration) However more rapid restoration of tonicity and volume can be achieved if part of the solution administered is in the form of hypertonic (2 or 3 per cent) sodium chloride This is *particularly indicated when there is evidence* of water intoxication

Hyponatremia with Increased Extracellular Fluid Volume Impairment of water excretion occurs commonly in situations in which there is also a reduction of the excretion of sodium salts The stage is thus set for a reduction of the osmotic pressure of body fluids—and the plasma sodium concentration—at the same time that the volume and total sodium content of the extracellular fluid is expanded The extent to which simple dilution or various combinations of dilution and expansion of extracellular fluid may ensue depends on the relative intakes of salt and water

In most *postoperative* patients the tendency to retain both salt and water is present The administration of excesses of isotonic saline solution may lead to edema However because of the recognized danger of producing edema (particularly in those who have undergone cardiac surgery) the administration of salt is often kept low while with an overestimation of the fluid needs of such patients large volumes of 5 per cent glucose are given Hyponatremia is the predictable result of such overtreatment This particular type of hyponatremia is easily avoided if its pathogenesis is understood When it has been inadvertently produced it is generally best treated by a reduction of fluid intake to the lowest feasible level so that insensible water loss and the minimal urinary losses of water can effect a return of the osmotic pressure of body fluids to normal If there is evidence of water intoxication the administration of hypertonic solutions may be required

Hyponatremia is commonly encountered in *edematous patients* with cardiac decompensation cirrhosis with ascites or the ne

phrotic syndrome Such patients have been erroneously considered to be salt depleted and the designation 'low salt syndrome has been misleadingly applied While it is true that those patients who develop hyponatremia have usually been subjected to restricted salt intakes and have frequently been given diuretics the cardiac patients most likely to develop dilution of the body fluids are generally almost unresponsive to diuretics In fact the hyponatremia often tends to disappear when responsiveness to diuretics is reestablished Undoubtedly the universal practice of relying in the treatment of edematous patients upon restriction of sodium intake while allowing a free intake of fluid contributes to the frequency of hyponatremia with edema The long held belief that a large fluid intake is beneficial to any sick person is also a contributory factor Whereas the person with a normal sensorium and the capacity to express his needs can be expected to satisfy his thirst when dehydrated he can not be relied upon to abstain from drinking fluids when he becomes diluted Fluid intake is largely a matter of habit

When hyponatremia develops in an edematous person restriction of water intake to the lowest level compatible with the comfort of the patient is indicated (In fact it might well be considered whether some restriction of water intake should not be imposed upon all patients subjected to limited salt intake for the prevention or treatment of edema even though this would include many able to maintain water balance on an unrestricted intake) The major therapeutic efforts should be directed against the underlying disease *Hypertonic salt solution should not be administered* because it increases the edema and further complicates the problem of therapy

Hypernatremia is without exception indicative of an increased effective osmotic pressure of the body fluids and is due to failure of water intake to keep up with losses It occurs almost exclusively in those who because of clouded sensorium or inability to communicate are unable to obtain sufficient water Diabetes insipidus with excessive losses of water in the urine may be a contributing factor particularly in those who have suffered head injuries—a group in whom hypernatremia is most frequently encountered Treatment should be aimed at an adequate water intake by mouth if possible and intravenously as 5 per cent glucose solution if necessary If the hypertonicity of the plasma is accompanied by a dilute urine diabetes insipidus is almost certainly present and should be treated by the administration of pituitary antidiuretic hormone If an aqueous solution is administered it must be given at frequent and regular intervals (0 5 to 1 0 units of vasopressin every three hours) Solutions of vasopressin tannate in oil can be used to maintain continuous antidiuresis (2 to 5 units every two to three days) When vasopressin is used particularly the long acting preparations caution must be used to avoid the administration of excessive amounts of water The amounts given should be just sufficient to reduce the plasma sodium concentration to normal and to maintain it at that level

Hypokalemia

Interpretation The plasma potassium concentration requires consideration in two respects first because the level of potassium in the extracellular fluid has a direct effect on certain functions especially muscular (including cardiac) and neuromuscular and second because taking into consideration certain factors which influence the distribution of potassium within the body the plasma potassium concentration can be a useful index of the presence of deficits or excesses of body potassium

Since only a small part of the body potassium is contained in the extracellular fluid marked changes in the potassium concentration of this compartment can occur with shifts into and out of cells involving relatively small changes in the potassium content of the cells Potassium tends to move into cells with cell growth and nitrogen deposition and to move out as cells are destroyed or in those situations usually associated with negative nitrogen balance Potassium moves into cells when glycogen is deposited and out of cells when it is broken down The equilibrium between extracellular and intracellular potassium is shifted toward the cells in alkalosis so that the plasma potassium falls as extracellular *p*H rises conversely in acidosis the plasma rises as a result of the shift of potassium out of cells On the other hand the plasma potassium is not greatly affected by changes in the volume of extracellular fluid while the plasma potassium may be temporarily diluted by rapid expansion of the extracellular fluid volume the tendency to maintain a constant ratio of intracellular to extracellular concentration rapidly restores the plasma potassium concentra

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tubule for exchange with potassium On the other hand although aldosterone secretion may be as great in patients with severe cardiac failure or cirrhosis as in those with aldosterone secreting tumors the cardiac or cirrhotic patient develops little or no potassium depletion because the relatively complete retention of salt leaves little sodium for exchange with potassium However when urinary electrolyte excretion is forced by the administration of diuretics large and rapid losses of potassium may be produced

Potassium depletion is thus most likely to be encountered in situations in which excessive adrenal steroids are present—as a result of the presence of hormone secreting tumors or following the administration of exogenous steroids under conditions of stress and trauma as in postoperative patients and in diabetic acidosis following the response to diuretics in edematous patients with salt losing kidney lesions as in renal tubular acidosis when there are large losses of gastrointestinal fluids (particularly if renal losses are accelerated by administration of more saline solution than absolutely required) and when large amounts of ion exchange resin are administered to salt retaining patients

Prevention and Treatment In many instances potassium depletion can be prevented by recognition of circumstances likely to lead to its occurrence In patients given adrenal steroids potassium depletion can be largely avoided by sharp restriction of sodium intake and if necessary by supplementation of the normal dietary potassium intake with 5 to 10 gm of potassium chloride per day In patients losing large volumes of gastrointestinal fluids the development of potassium deficits should be anticipated if the losses are continued beyond a few days if the parenteral route is the only possible means of administration potassium chloride should be added at a concentration not in excess of 50 mEq per liter to be administered at a rate not exceeding 15 mEq per hour The parenteral administration of potassium is hazardous because of the cardiac effects of a high plasma potassium and if potassium is administered too rapidly cardiac effects may be precipitated even in the depleted patient Parenteral administration should be avoided if potassium containing fluids or better a normal diet possibly supplemented with potassium chloride can be given by mouth The advantages of restriction of sodium intake in facilitating the replacement of potassium deficit should be recognized When potassium is administered parenterally it is advisable to follow the electrocardiogram for changes characteristic of potassium intoxication and if possible to obtain frequent determinations of the plasma potassium concentration Potassium should not be administered unless there is an adequate level of renal function

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Acidosis

Definition Acidosis is an abnormal condition caused by the accumulation in the extracellular fluids of excess acid (hydrogen ions) or by the loss from the body of alkali (substances like bicarbonate which bind hydrogen ions) The more common cause is the accumulation of acid that is a state in which acids are formed or absorbed more rapidly than they can be destroyed or eliminated This process may be considered to have produced a state of acidosis when it has caused either the bicarbonate of the blood to fall or the hydrogen ion concentration to rise above the normal limits

Etiology Acidosis is a symptom complex not a disease in itself Acidosis of clinical importance is observed chiefly in diabetes * renal disease certain diarrheas cyclic vomiting in children and poisoning by salicylates or methanol

Severe acidosis may complicate implantation of the ureters into the sigmoid colon It may also occur in pulmonary emphysema bronchitis or extensive fibrosis from impaired pulmonary exchange of gases

Physiology and Chemistry The body fluids are mildly alkaline and even in the most extreme acidosis compatible with life they remain on the alkaline side of neutrality *i e* in acidosis the body becomes more weakly alkaline than normal Reaction (degree of acidity or alkalinity) of fluids is customarily noted in terms of pH which is the negative logarithm of the H ion concentration The H ion concentration of blood is something less than one ten millionth normal It may be described as having a hydrogen ion concentration of $10^{-7.4}$ or more conveniently as having a pH of 7 4 In adopting this logarithmic form of expression however it must be realized that a fall in pH from 7 4 to 7 2

* Diabetic acidosis is discussed in detail in the section on Diabetes

tion to very nearly the level existing before the expansion

In interpreting the significance of a particular concentration of potassium in the plasma and whether or not the administration of potassium is likely to be indicated some consideration must be given to these factors affecting the distribution of potassium within the body For instance the patient in diabetic acidosis may be found to have a high plasma potassium but taking into account the fact that restoration of the blood pH to normal and reconstitution of depleted glycogen stores will both cause a shift of potassium into cells it may be seen that the plasma potassium is certain to fall even if there are no further external losses and that this fall may well carry below the normal range

Effects of Hypokalemia It is sometimes difficult to distinguish the results of reduced extracellular potassium concentration itself from those due to potassium depletion since the two are so often associated The most striking symptom of hypokalemia muscular weakness which may progress to paralysis of the extremities and eventually to impairment of respiratory movements is clearly associated with the depressed extracellular potassium concentration and although it may be associated with potassium depletion it can occur without external potassium losses as in periodic paralysis The electrocardiographic changes associated with hypokalemia prolongation of the Q T interval depression of the S T segments and flattening of the T waves are also the result of the reduced extracellular potassium A reduced plasma potassium concentration also potentiates the effects of digitalis glycosides and in the digitalized patient digitalis toxicity may be precipitated by potassium losses leading to hypokalemia A number of symptoms and signs associated with hypokalemia combined with potassium depletion are probably dependent largely on the latter or on both apathy distention or even paralytic ileus alkalosis and depression of renal function Necrosis and hyalinization of cardiac and skeletal muscle fibers and vacuolar lesions in the renal tubules are observed with more severe grades of potassium depletion

The plasma potassium concentrations at which various effects are observed vary widely in different persons and from time to time The reasons for this are not entirely clear It is sometimes stated that it is the ratio of extracellular to intracellular potassium concentration which is the important variable This ratio is under most conditions very difficult to determine However it should be noted that the concentration changes in extracellular fluid are virtually always greater than those in intracellular fluid so that a reduced plasma potassium almost always means a low extracellular to intracellular concentration ratio and an elevated plasma potassium the reverse

Pathogenesis Factors which may produce a lowered plasma potassium by internal redistribution have already been discussed In most instances significant hypokalemia is the result of external losses of potassium through losses of gastrointestinal fluids urinary excretion or both Potassium is present in all the gastrointestinal secretions at concentrations higher than in extracellular fluid so that continued loss of such secretions may account for considerable potassium deficits These gastrointestinal losses are likely to be the more significant because they are often associated with complete interruption of potassium intake and because they are often accompanied by continuing losses of potassium in the urine for reasons to be discussed

Although the kidney is capable of decreasing potassium excretion to very low levels when under no stress other than reduced potassium intake with mild consequent potassium deficit potassium excretion under other stresses often remains at an inappropriately high level because of the necessity to excrete some electrolyte under conditions where there are strong stimuli to retain sodium This usually involves the effect of adrenocortical steroids on renal electrolyte transport with substitution of potassium for sodium in the urine

The renal effect of adrenal steroids pertinent to the production of potassium losses is upon the exchange of potassium and sodium ions In order that potassium ions be secreted into the urine it is necessary that sodium ions be delivered to the site presumably in the distal tubule at which this exchange is effected Consequently potassium losses are relatively great when electrolyte output is large and may be small or absent if salt intake (and consequently chloride excretion) is markedly restricted or if because of accumulation of most of the sodium intake in the form of edema the output of electrolyte in the urine is low Thus potassium depletion is marked in primary aldosteronism because sodium intake continues and net sodium retention is virtually negligible Thus plenty of sodium is available at all levels in the renal

neys with apparently normal glomerular function may lack the normal tubular function of acidification with resulting acidosis The inability to acidify the urine together with the increased urinary excretion of calcium in acidosis may produce osteoporosis and nephrocalcinosis Other renal tubular functions such as production of ammonia and reabsorption of glucose phosphorus potassium and amino acids may also be defective in such patients

Starvation acidosis is of especial importance since it plays an important role as a complicating factor in disease It is due to unavailability of preformed carbohydrates and can be produced as well by severe restriction of carbohydrate intake as by complete starvation The reduction of bicarbonate is due to displacement by abnormal amounts of ketone acids The increased ketone production is related to increased utilization of fat as it is in diabetes

The acidosis of *cyclic vomiting* of children is largely if not entirely the result of starvation ketosis to which children are particularly susceptible

Loss of alkaline intestinal fluids in considerable volumes may lead to acidosis This seldom reaches important proportions except in Asiatic cholera in which large amounts of liquid alkaline fluid may be passed and in some of the diarrheas of infancy Losses of biliary or pancreatic secretions by fistulas or surgical drainage may likewise produce acidosis Starvation by increasing ketone production and dehydration by impairing the base sparing functions of the kidneys enchance the acidosis

The *ingestion of ammonium chloride* produces acidosis because the ammonia is quantitatively converted to urea in the liver leaving chloride ion to displace bicarbonate from the plasma Ingested calcium chloride produces a similar effect because calcium is largely excreted by the gut in combination with phosphate carbonate and soaps while the chloride remains to encroach upon plasma bicarbonate Both ultimately affect plasma bicarbonate just as hydrochloric acid would

Acetazolamide a diuretic drug which inhibits carbonic anhydrase causes acidosis by slowing the rate at which hydrogen ion can be secreted by the renal tubules thereby reducing the excretion of ammonium ion and titratable acid and increasing greatly urinary losses of bicarbonate

Severe hyperchloremic acidosis may occur as a complication of ureterosigmoid anastomoses This is due largely to absorption of ammonium salts from the bowel

Pulmonary or circulatory diseases which interfere with the exchange of gases between blood and alveolar air may produce acidosis by allowing an abnormal accumulation of carbon dioxide in the body There is a compensatory increase in serum bicarbonate which tempers the decrease in *p*H The increase in serum bicarbonate is effected by augmented tubular reabsorption of bicarbonate in response to elevated carbon dioxide tension

The respiratory centers demonstrate diminished sensitivity to change in *p*H or *p*CO during prolonged hypercapnia Under these circumstances decreased oxygen tensions may displace acidosis as the dominant determinant of respiratory ventilation Exposure to high concentration of oxygen by diminishing anoxia may provoke intolerable acidosis

Acidosis commonly complicates diseases which quite apart from acidosis are characterized by severe dehydration Thus in diarrheas and cyclic vomiting loss of intestinal contents leads to severe dehydration in itself In nephritis and diabetes polyuria vomiting and excessive loss of water through pulmonary ventilation all contribute to dehydration The fluids of the body become so depleted that blood volume may fall below the point at which the circulation can be supported

The larger part of the base lost is sodium This comes almost entirely from the extracellular fluids which also yield variable amounts of water so that the concentration of sodium in plasma and extracellular fluids may be reduced normal or even occasionally elevated Variable amounts of the normal small intracellular component of sodium leave the cells during acidosis and contribute to the over all sodium loss

Considerable amounts of potassium the major intracellular base are also lost during acidosis The effect on plasma potassium will depend to a large extent on the intake of potassium the severity of dehydration and the functional status of the kidneys Thus in advanced renal disease with obligatory polyuria treated with fluids lacking in potassium the concentration of potassium may be subnormal in plasma as well as in cells This is true also in primary renal tubular dysfunction in which reabsorption of potassium as well as secretion of acid may be impaired In most instances of acidosis however accompanied as they are by oliguria the discharge of potassium from cells results in elevated plasma potassium This is especially pronounced if excessive protein breakdown and glycogen

represents a doubling of H ion concentration The extremes of pH encountered in disease are something of the order of 7 0 and 7 7

Normal body function depends on maintence of the reaction of body fluids within relatively narrow limits between pH 7 35 and 7 45 This regulation is dependent on the buffer properties of blood and other body fluids regulation of carbon dioxide excretion by the lungs and renal function

Buffer Effect Substances which by their presence in solution decrease the pH change caused by the addition of acid and alkali are called buffers They are mixtures of a weak acid and its alkali salt or of a weak base and its acid salt The buffers of physiological importance are mixtures of weakly dissociated acids and their strongly dissociated salts Those of significance are carbonic acid and $BHCO_3$ * B_2HPO_4 and BH_2PO_4 proteins (including hemoglobin and tissue protein) with base proteinate and organic phosphates with their basic salts Together these comprise approximately one third of the alkali normally present in plasma and probably a greater fraction of the alkali of the cells of the body

Respiratory Regulation In any mixture of a weak acid and its salt the pH of the solution is determined by (and in turn determines) the ration of free acid to salt in the mixture The reaction of blood therefore depends on the ration of free carbonic acid to bicarbonate $\frac{H_2CO_3}{BHCO_3}$ which at normal pH of 7 35 is about 1 20 The concentration of carbonic acid in this equation *is directly related to the carbon dioxide* tension in the blood Since carbon dioxide which is constantly formed in abundance in cellular oxidations is excreted through the lungs the carbon dioxide tension may be altered rapidly by change in respiration Other factors being constant the carbon dioxide tension of the blood decreases with deep respiration and increases with shallow respiration The carbonic acid bicarbonate buffer is thus much more effective *in vivo* than *in vitro* since in the latter the addition of strong acid causes a comparable increase in carbonic acid while in the former carbonic acid becomes decreased below its original level through increased pulmonary ventilation The appropriate change in ventilation is determined by the medullary respiratory center in response to pH and pCO_2

Renal Regulation The metabolism of the ordinary diet yields phosphoric and sulfuric acid equivalent to 400 to 800 ml or more of tenth normal acid If this were excreted as neutral sodium salts the body would rapidly be depleted of cation This is normally excreted by the following mechanisms First the renal tubules synthesize ammonia which combines with secreted hydrogen ion to convert the sodium salts of glomerular filtrate into ammonium salts thereby removing hydrogen ion from the body Second the renal tubules convert the slightly alkaline glomerular filtrate into acid urine which permits the excretion of weak acids such as uric citric and beta hydroxybutyric in the free form The cells of the distal tubules derive the hydrogen ions for this purpose from carbonic acid which they can form rapidly from carbon dioxide by the action of carbonic anhydrase The most acid urine which the kidney can elaborate has a pH of 4 5 at which reaction no significant amounts of strong acids such as sulfuric or hydrochloric can exist in free form Hence base can be spared in the excretion of these acids only by substitution of ammonia Finally the secretion of hydrogen ions in exchange for sodium by the renal tubules permits the complete absorption of bicarbonate from glomerular filtrate thus insuring against the loss of cation (bicarbonate) in the urine

Pathological Physiology and Chemistry The abnormally high H ion concentration of acidosis is almost always the result of decrease in the denominator of the carbonic acid bicarbonate ratio This decrease in bicarbonate is however never a primary event It is always caused by the accumulation in the body of an excess of acid other than carbonic or by the loss from the body of alkali more commonly the former

In the acidosis of *advanced renal disease* bicarbonate is reduced chiefly by accumulation of abnormal amounts of phosphoric sulfuric and organic acids Poor food intake and vomiting may increase ketone production A further factor encroaching upon bicarbonate is diminution of the sodium of plasma by failure of the renal mechanisms for conservation of base in excreting acids The ability of the damaged kidney to acidify the urine and to form ammonia is much impaired The base conserved by these mechanisms in the acidosis of advanced nephritis is a small fraction of that saved by these mechanisms in diabetic acidosis of comparable degree Kid

* B = base (sodium or potassium)

sium deficit Physiological saline solution is of prime importance to replace losses of water and electrolytes by parenteral routes Approximately 80 ml per kilogram of body weight is necessary to correct severe de hydration Half of this should be given within the first hour or two if possible and the remainder in the course of the next few hours Sufficient glucose (or fruc tose or invert sugar) must be supplied to reduce protein breakdown and excessive ketone formation For this purpose at least 2 gm per kg of body weight should be given daily and it is probably advisable to give twice this much This may be given as 5 or 10 per cent solution intravenously until oral feeding becomes possible The glucose should be given in distilled water unless the plasma sodium is subnormal in which case it may be given in physiological saline solution

Alkali may be used to speed relief of hyperpnea in the acidosis associated with diarrhea especially in infants in whom the renal regulatory mechanism is incompletely developed Alkali may be given as bicar bonate (2 to 5 per cent) or lactate (one sixth to one half molar) intravenously In the body lactate is converted to glycogen leaving sodium available for neutral ization of acid Patients with acidosis severe enough to provoke recognizable hy perpnea may be given 7 ml of 4 per cent bicarbonate (or 25 ml of one sixth molar lactate) per kg of body weight with im punity It is rarely necessary to give more to relieve the hyperpnea and it matters little if plasma bicarbonate is not restored to normal levels immediately Various prep arations containing sodium potassium bi carbonate (or lactate) and chloride in proportion to those found in normal intes tinal fluids are available commercially These may be substituted freely if desired for physiological saline in replacing current losses of intestinal fluids

Massive infusions of physiological saline solution may be given subcutaneously with impunity If the circulation is adequate this is absorbed with extreme rapidity by the severely dehydrated patients as much as 3 liters being commonly absorbed within two hours Failure of the severely dehy drated patient to absorb subcutaneous fluid rapidly denotes circulatory collapse and is an indication for prompt blood transfu sion or administration of plasma Glucose solutions should not be given subcutane ously since they cause a temporary net loss of available salt to the tissue because salt diffuses into them more rapidly than glu cose diffuses out All these considerations unimportant as they may seem in most cases may be important in individual cases in tipping the balance into circulatory col lapse which is a prime threat to life If any evidence of shock is present blood plasma or plasma substitute should be given without delay

The parenteral administration of potas sium serves to minimize the risk of serious depression of plasma potassium during treatment with parenteral fluids and glu cose and also speeds the restoration of normal cellular potassium The potassium should not be given at the start of treat ment when plasma potassium is commonly normal or elevated lest plasma potassium rise to the point at which fatal heart block ensues (approximately 10 mm per liter) Ideally it should be given only after a sharp depression of plasma potassium has been demonstrated by analysis In the ab sence of facilities for such analyses evi dence of subnormal potassium levels may be detected by electrocardiographic changes These are in order of their appearance prolonged Q T interval low T waves sag ging S T segments and depressed S T take-off the last occurring at levels of 1 5 mm or less In any event potassium should not be given until sufficient saline and if necessary blood or plasma is given to insure adequate circulatory status and urine flow If neither chemical determina tions nor electrocardiograms are available it is probably safe to give potassium six to eight hours after the start of therapy unless shock or anuria is present For gen eral use it is probably safest to use con siderably less than the maximal amount of potassium tolerated It is suggested that 0 1 to 0 15 gm of potassium chloride per kg be given intravenously over a period of not less than four hours When feed ing is resumed there is no clear indi cation for supplementary potassium since most foods contain it in abundance al though in the opinion of some complete recovery is speeded by the addition of po tassium salts to the diet If feeding can be resumed within six to eight hours of the start of treatment it is probably desirable to dispense with the parenteral administra tion of potassium since both fruit juices and milk as well as most other foods con tain considerable potassium and supple mentary potassium chloride can be given by mouth if desired The risk however slight of producing fatal elevation of plasma potassium by parenteral admin istration is thus avoided

depletion add to the release of potassium from cells or if circulatory collapse is present During treatment with large amounts of fluid and glucose however plasma potassium falls sharply as a result of continued urinary loss dilution by expansion of extracellular fluid volume and transfer into cells during resumption of carbohydrate utilization In infantile diarrhea or diabetic acidosis for example serum potassium frequently falls below 2 millimols per liter during intensive treatment with parenteral glucose water and salts other than potassium Muscular paralysis cardiac abnormalities and even death have been attributed to this fall in plasma potassium Acidosis decreases neuromuscular excitability There is some evidence that it impairs utilization of carbohydrate Chronic acidosis may produce severe decalcification of bones with pathological fractures It presumably affects many other functions to varying degrees

Calcium is also wasted in acute acidosis plasma levels being maintained by transfers from bone In some circumstances during treatment of infantile diarrhea with parenteral fluids serum calcium may fall to a degree which produces tetany and possibly other serious derangements

Symptoms Mild acidosis has no recognizable symptomatology Hyperpnea tachycardia drowsiness nausea stupor and coma are characteristic of severe acidosis Of these only hyperpnea is unequivocally related to the acidosis *per se* Respiration is extremely deep and the rate is increased Overventilation usually becomes apparent when the bicarbonate falls to 30 volumes per 100 ml but does not become severe until it falls below 20 volumes per 100 ml In the terminal state respiration becomes weak and irregular Whether or not the cerebral symptoms can be related to acidosis has not been established It seems probable that circulatory changes secondary to the severe dehydration which regularly accompanies acidosis play an important role In support of this hypothesis is the similar mental picture observed in the shock or impending shock of severe dehydration in diseases in which acidosis is not present also in the observation that drowsiness may often be alleviated by transfusion or fluid administration before there has been any relief of acidosis It seems probable that accumulation of ketone bodies plays a part in the production of the cerebral changes in diabetic acidosis

Diagnosis Mild acidosis cannot be recognized clinically but may be diagnosed by determination of serum or plasma bicarbonate Values between 30 and 55 volumes per 100 ml indicate mild acidosis Severe acidosis is recognized by the extraordinary air hunger The breathing is deep and rapid The diagnosis may be confirmed by determination of the carbon dioxide content combining power or the *p*H of plasma Hyperpnea dehydration and drowsiness even without any available history should suggest diabetes which may be confirmed by the presence of sugar and acetone in the urine

Detection of acidosis in patients with abnormal loss of alkaline intestinal secretions or with ureterosigmoid anastomoses depends on suspicion of the possibility In renal disease severe acidosis is manifest by hyperventilation but moderate acidosis of long duration may be asymptomatic Awareness of this possibility in patients with dwarfism or with unexplained decalcification of the bones may lead to the primary diagnosis of chronic renal disease especially the type with renal tubular dysfunction in which the urine may be free of albumin

Prognosis Death probably never results from acidosis *per se* The prognosis depends first upon that of the underlying or complicating disease and second upon the state of the circulation The outlook of the patient with the acidosis of advanced renal insufficiency is understandably poor Recognition of asymptomatic acidosis in renal disease may improve prognosis in respect to decalcification of bones and may initiate therapy to accelerate growth if retarded The outcome of acute diarrhea or cyclic vomiting is dependent less on the degree of acidosis than on the extent to which the circulation has been compromised by loss of water and salt and on the degree to which depletion of potassium has progressed Sudden deaths during apparently successful therapy of infantile diarrhea have been ascribed to the development of subnormal levels of potassium in the plasma Prognosis is improved by the prompt use of blood or plasma in combating circulatory collapse and by supplying potassium at the proper time A rapidly fatal outcome in the acidosis complicating ureterosigmoidostomy is readily averted by simple measures

Treatment In acidosis due to excessive loss of alkaline intestinal secretions in diarrheal stools or from fistulas or surgical drainage correction of the acidosis is usually less urgent than that of dehydration circulatory collapse starvation and potas

ences of alkalosis and hypocalcemia are additive however is demonstrated by amelioration of hypocalcemic tetany by administration of acid or acidifying salts and by the precipitation of tetany in hypercalcemic terminal nephritics by alkali administration

In alkalosis the cells contain subnormal amounts of potassium and excessive amounts of sodium This disturbance of composition is not necessarily associated with abnormal concentrations of sodium and potassium in the serum

Symptoms The symptoms of alkalosis are those of the underlying disease plus those of tetany Tetany is discussed in details elsewhere in this volume

Diagnosis If the possibility of alkalosis is entertained in patients with vomiting and tetany diagnosis presents no difficulty The plasma bicarbonate is markedly elevated (to as high as 140 volumes per cent) and plasma chloride proportionately reduced Serum calcium is within normal limits In patients receiving alkali for gastric acidity alkalosis should be suspected when vomiting increases or evidence of renal insufficiency develops even in the absence of tetany and confirmation should be sought by determination of plasma bicarbonate Tetany in the presence of hyperventilation should suggest alkalosis If this is of brief duration as in sighing or hysterical breathing plasma bicarbonate and serum calcium are both within normal limits In more prolonged hyperventilation as in disease of the central nervous system plasma calcium is *again normal* but bicarbonate may be subnormal Thus we have the paradoxical situation in which hyperventilation and reduction of plasma bicarbonate accompany alkalosis and not acidosis Determination of *pH* will of course make the differentiation but this is usually not necessary if the possibility of alkalosis is entertained in such cases and the usual causes of acidosis are excluded

Prognosis The prognosis is that of the disease which it complicates Severe tetanic spasms of the larynx or skeletal musculature may contribute to a fatal outcome

Treatment The alkalosis which results from loss of acid secretions requires treatment no more urgently than does the accompanying dehydration starvation and potassium depletion Carbohydrate must be supplied to reduce ketosis and protein wastage and precautions taken against circulatory collapse as described for acidosis Approximately 80 ml of fluid per kg of body weight is required to correct severe dehydration In most instances physiological saline suffices chloride being selectively retained by the kidneys If tetany is severe *ammonium chloride may be given initially* (2 to 500 ml of 2 per cent solution) along with physiological saline intravenously but this is rarely necessary Sodium chloride in itself can restore extracellular fluid volume but cannot fully correct the alkalosis until replacement of cellular potassium is effected The latter provokes transfer of hydrogen ions from cells to extracellular fluids and permits the kidneys again to elaborate an alkaline urine thus sparing hydrogen ions for correction of extracellular alkalosis Potassum is required in large amounts not only to prevent the consequences of hypokalemia (as described under acidosis) but more important to correct fully the large cellular deficit Retention of more than 500 mEq (38 gm of potassium chloride) may occur during treatment When urine flow is good there is no risk in giving large amounts of potassium parenterally or orally It is of course desirable to control treatment by analysis of the serum for potassium and to follow electrocardiograms as described for the treatment of acidosis

In hyperventilation tetany treatment of the underlying disease is the prime indication Breathing mixtures of 5 per cent carbon dioxide in oxygen will afford relief of the tetany of primary *hyperventilation* though this is hardly necessary in the hysterical group

P H LAVIETES

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Renal Acidosis Acidotic hyperpnea should be allayed if possible by administration of alkali This may be tolerated by mouth but more often must be given intravenously (as 4 per cent bicarbonate or one sixth molar lactate) It is neither necessary nor desirable to restore the plasma bicarbonate to normal Attempts *to do so may precipitate tetany or edema* In the hyperpneic patient 7 ml of 4 per cent bicarbonate or 25 ml of one sixth molar lactate per kg of body weight may be given slowly This must be repeated if hyperpnea persists or recurs Smaller doses seldom give any relief If tetany supervenes administration of alkali must be slowed or stopped if severe especially with laryngospasm 1 gm of calcium chloride should be injected slowly intravenously (as 10 per cent solution) and repeated if necessary Asymptomatic reduction of serum bicarbonate may be treated by daily doses of sodium bicarbonate or citrate sufficient to correct the deficit partially (2 to 6 gm daily in divided doses) If heart failure makes the use of sodium salts undesirable the potassium salts may be substituted provided of course serum potassium is not considerably elevated

The use of alkali is imperative in those cases of primary renal tubular disease in which prolonged though often asymptomatic acidosis contributes to the production of osteoporosis These patients should also receive supplements of calcium lactate (2 to 4 gm daily) and vitamin D (50 000 units daily) Some patients with renal tubular defect waste potassium sufficiently to cause muscular weakness and electrocardiographic abnormalities Large supplements of potassium may prove necessary to compensate for this deficiency

The acidosis of ureterosigmoidostomy is corrected by salt restriction supplements of sodium bicarbonate or citrate and care to evacuate the rectum frequently

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Alkalosis

Definition Alkalosis is an abnormal condition caused by the accumulation in the extracellular fluids of an excess of alkali or by the loss of acid (hydrogen ions) more commonly the latter The bicarbonate of the blood is increased (with one exception which is described later) and its hydrogen ion concentration is diminished

Etiology Alkalosis may occur from excess alkali intake It also follows loss of acid secretions from vomiting or gastric suction Depletion of body potassium which accompanies the above in itself provokes alkalosis Presumably the intracellular po*tassium ions lost are replaced by hydrogen* ions from the extracellular fluids Alkalosis secondary to loss of potassium is seen commonly in patients with biliary and intestinal fistulae severe diarrhea and in patients maintained for long periods of time on parenteral feedings without added potassium as well as in patients secreting or receiving large amounts of adrenal cortical hormones Alkalosis may result from loss of carbonic acid through hyperventilation in response to functional or organic disease of the central nervous system or to anoxemia

Pathological Physiology and Chemistry Alkalosis due to excessive loss of acid and potassium in intestinal secretions is always accompanied by severe dehydration Paradoxically urine is usually acid in this situation since secretion of hydrogen ions by the kidney is promoted by potassium depletion as well as by the intense stimulus of dehydration to the reabsorption of sodium ions In alkali excess alkalosis change in *pH* is opposed by increase in carbon dioxide tension of the body fluids through diminished pulmonary ventilation Conversely the alkalosis of primary overventilation is tempered by decrease in the bicarbonate of the body fluids Renal tubular reabsorption of bicarbonate has been shown to be regulated by the carbon dioxide tension of the body fluids

The most striking manifestations of alkalosis are those of neuromuscular hyperexcitability These are indistinguishable from those of hypocalcemia though there is no clear evidence that they exert their effect indirectly through calcium That the influ

and frequently will cease to be fat after puberty True Frohlich s syndrome is exceedingly rare and difficult to diagnose before the normal age of onset of puberty

Then there comes the child who does not do well in school There is a feeling among would be progressive educators that such a situation demands a survey by an endocrinologist In the author s experience there is only one endocrine abnormality which leads to mental retardation namely cretinism The diagnosis of this condition is a problem for the obstetrician and the pediatrician not for the endocrinologist If it is not made in the first few weeks or at the most months of life the damage is already done and one might just as well not make the diagnosis Parenthetically it might be added that every physician should suspect cretinism in any child with an umbilical hernia at birth which persists after the first few weeks of life Even juvenile myxedema is not associated with retarded mentality To be sure long standing hypoparathyroidism leads to epileptic seizures and secondary mental retardation The author has seen in consultation a number of children with poor school records and to date has been unable to make a diagnosis of endocrine disease in any of them He is impressed by the fact that many of them have been "mirror readers "

Thirdly the author has yet to see a homosexual patient in whom the trouble was based on faulty endocrine function or in whom the giving of a hormone influenced the direction of the libido Of interest in this connection is an observation made by Dr Anne P Forbes and known in our clinic as "Forbes s law" A patient who complains of impotence or of lack of libido does not suffer from a hormonal lack a patient with real endocrine insufficiency *e g* eunuchoidism has impotence and absent libido but does not complain of them but of something more trivial such as being mistaken for a girl over the telephone

A fourth type of case sent to the endocrinologist is the patient with some congenital disorder of the germ plasm such as mongolian idiocy Laurence Moon Biedl syndrome and so on Just why such conditions should be confused with endocrinopathies is not clear It is probably connected with the belief that anything which is not fully understood belong to endocrinology

Finally there are the patients with alopecia areata The endocrines have some thing to do with certain types of hair these patients have too little hair there fore they are sent to the endocrinologist However the fact that this condition starts by being spotty is strong evidence against an endocrinological etiology It makes no difference that one spot may enlarge to the points where it covers the whole body the disease is still a "spotty" one Endocrinological diseases are generalized not localized hormones do not stop in the midline or proceed down one limb and not the other For example Paget s disease of bone is not endocrinological since it is not generalized Though it involves 95 per cent of the skeleton there will still be a sharp demarcation between the uninvolved part and the Paget s disease Postmenopausal osteoporosis on the other hand may be confined to the spine and pelvis and still be a generalized disease since here there is a rhyme and a reason to the distribution This discussion concerns the *primary* lesion produced by an endocrinopathy Secondary complications can be spotty (*e g* gangrene of the toe in diabetes bone cyst with hyperparathyroidism)

Failure of End Organs to Respond to Hormones Since a hormone acts somewhere it is obvious that one might get much the same clinical syndrome from failure of the end organ to respond to the hormones as one would get with absence of the hormone itself For example let us take "pseudohypoparathyroidism " Patients with this condition have the clinical and chemical findings that one associates with hypoparathyroidism but they fail to respond to parathyroid hormone and their parathyroid glands not only are not absent but may be hyperplastic A second example is the failure of the American Indian to develop a beard A patient presented himself his only complaint being failure to develop a beard Elaborate studies were carried out with uniformly normal results Finally someone had the wit to inquire about the patient s ancestry and found that he was part Indian

Oophorectomy The author feels that needless oophorectomy constitutes one of the greatest faults in medical practice A normally functioning ovary needless to say is most essential for the future physical and mental well being of a young woman Satisfactory as replacement therapy is it will not produce ova or be a substitute for motherhood

There are two chief reasons for unnecessary ovarian surgery The general surgeon does not realize that the normally functioning ovary is a cystic organ he performs an exploratory laparotomy for some

Diseases of the Ductless Glands

Introduction

The author will not write the conventional introduction He will not give the Greek derivation for the word hormone coined by Starling he will not discuss the experiments of Claude Bernard which led to the concept of an internal secretion he will not delve into the earliest beginnings of endocrinology which had as their *raisons d etre* such ends as the procurement of a form of manpower safe for the harem the salvaging of a male soprano voice for the choir the increased palatability that a rooster attains when he turns into a capon and so on He will not trace experimental endocrinology from 1849 when Berthold studied the effect of the gonads on the secondary sex characteristics of fowl for the next hundred years down to 1949 when attention was focused on cortisone and its pituitary stimulator adrenocorticotrophic hormone (ACTH) But why mention such prosaic facts in 1959 when we are well into the schizo atomic era and rapidly approaching the author fears the posthistoric era? It would be more in keeping to mention that a pellet of stilbestrol can now replace pregnancy as a promoter of lactation in cows No the author will not even list the names of describers of various endocrine syndromes —from Addison with Addison s disease in 1855 down past the almost simultaneous elucidation of hyperparathyroidism in 1926 both by Mandel and by Du Bois to—well—to whom? The author thinks of no recent unmasking of a new syndrome Are we leaving an era behind?

Instead he will discuss what endocrinology is with special emphasis on what endocrinology is not and then will comment on certain other aspects of the subject

What Endocrinology Is Endocrinology is an indivisible division of internal medicine and has to do with certain glands or tissues which secrete highly specific substances into the blood stream for use by other tissues The only important thought in this definition is contained in the word indivisible It is impossible to separate endocrinology from internal medicine by the same token it is impossible to be an endocrinologist without being an internist The physician who calls himself an endocrinologist and confines his interest to such unfortunate members of society as might appear in the sideshow of a circus never realizes that pneumonia a broken leg and a bad burn involve important changes in adrenal cortical function (cf Alarm Reaction of Selye) that the disturbance in homeostasis occasioned by chronic renal insufficiency is ameliorated by a secondary hyperparathyroidism that the somatotrophic action of testosterone propionate may be made use of in many conditions other than male hypogonadism and so on

The author resents the tendency to limit the scope of endocrinology to those disorders of the internal secretions which are not clearly understood Thus once some division of endocrinology such as diabetes is put on a firm footing it is removed from the section on endocrinology to the section on metabolic diseases

What Endocrinology Is Not Certain conditions often considered to be endocrinological are probably not so at all

First in order of frequency comes the fat boy who is slightly late in sexual development and whose genitalia are obscured by excess of fat This patient nine times out of ten is labeled as having Frohlich s syndrome whereas in point of fact he is just a fat boy whatever that is *If left* alone he will develop normally sexually

DISEASES OF THE THYROID GLAND

Normal Physiology of the Thyroid Gland

The functions of the thyroid glands are to synthesize store and secrete the thyroid hormones The processes involved in these functions are complex and incompletely understood but it is now possible to measure the changes which are characteristic of various diseases of the thyroid Modern knowledge of thyroid physiology can be traced largely to two new experimental tools radioactive iodine and certain drugs such as thiourea which have specific effects upon the thyroid gland

The metabolism of iodine is intimately involved in thyroid physiology The daily ration of iodine which is normally between 100 and 250 micrograms is absorbed from the gastrointestinal tract as iodide Thyroxine and triiodothyronine if ingested may be absorbed unchanged The thyroid selectively concentrates iodide from the blood This energy requiring process is specifically blocked by certain inorganic radicals such as perchlorate and thiocyanate Trapped iodide is quickly oxidized and transferred to tyrosyl residues in peptide linkage within the thyroid parenchymal cells to form mono and diiodotyrosine These iodinated residues in turn are condensed to triiodothyronine and thyroxine which are then stored in the thyroid colloid The colloid is composed of a complex glycoprotein of high molecular weight (*circa* 600 000) called thyroglobulin which contains the iodinated amino acids as part of the amino acid sequence It is degraded to its constituent amino acids by proteolytic enzymes which are thought to be activated by the thyrotropic hormone of the anterior pituitary At the same time mono and diiodotryrosine are also released from peptide linkage these substances do not reach the peripheral blood but are degraded by a potent deiodinating enzyme which is present in the thyroid parenchymal cells Normally the thyroid releases 75 to 125 micrograms of hormonal iodine daily

Thyroxine which reaches the blood is transported in close association with a protein which has an electrophoretic mobility close to that of α globulin A small fraction also is associated with albumin Triiodothyronine is less closely bound to plasma protein The quantity of hormonal iodine in the peripheral blood is normally between 3 5 and 8 0 micrograms per 100 ml Probably more than 80 per cent of this is thyroxine and the rest triiodothyronine

The biochemical nature of the action of the thyroid hormones on peripheral cells is unknown *In vitro* studies suggest that thyroxine may cause its metabolic effect by dissociating oxidative phosphorylation so that oxidation proceeds without the concomitant formation of phosphate bond energy The thyroid hormones are largely deiodinated by the peripheral cells and iodide is returned to the blood for recirculation Some of the thyroxine and triiodothyronine are formed into their respective glucuronides and are secreted in the bile The acetic acid derivatives of thyroxine and triiodothyronine have been detected in brain and kidney but their precise role in metabolism is not known

Iodide is excreted by the kidney at a clearance rate of approximately 35 ml of plasma per minute The thyroid clears iodide at a slightly less rapid rate under normal circumstances The kidney does not alter its clearance rate over wide ranges of iodide supply but the thyroidal clearance is sensitive to the mean daily intake of iodide Adjustment to a changed mean level of intake is not reached by the thyroid until many weeks have passed

Thyroxine and triiodothyronine (3 5 3 triiodothyronine) are thought to be the definitive thyroid hormones and the only significant secretion products of the gland There is evidence however that 3 3 diiodothyronine and 3 3 5 triiodothyronine are also secreted by the thyroid but these substances are extremely rapidly degraded Thyroxine and triiodothyronine have the same physiological effects qualitatively but quantitatively there are striking differences The effect of thyroxine is not ob

sort of abdominal pain and finds nothing but cystic ovaries out they come For some reason the surgeon is never sued for mal practice because of this the story would be different if under somewhat analogous conditions *castration were resorted to in* the male

Metropathia hemorrhagica is the second big cause for unnecessary removal of the ovaries This interesting condition can be treated medically in almost all instances

The author disapproves of oophorectomy even after the menopause He feels that the ovary still functions to a certain extent after the periods have ceased and that one sees more severe osteoporosis after an arti ficial menopause than after a physiological one

Fat Distribution Considerable space has been wasted in textbooks and writings on endocrinology about the distribution of fat In the writer s opinion there are fat people and thin people but with one exception the distribution of fat is of no diagnostic significance The one exception is in Cush ing s syndrome in which there is a tendency for the face to be round (moon faced) this roundness is probably due to a tendency to deposit fat in front of the ears How ever that a propensity to deposit fat around the hips or on the lower extremities or diffusely throughout the body or where you will has any diagnostic significance is most unlikely it almost certainly has nothing to do with pituitary disease

Hirsutism without Virilism Of the many thorns in the side of the endocrinologist the most aggravating is the patient whose life is made miserable by excessive hair growth on the face and elsewhere In only one case in a hundred can the physician find an endocrine fault and what is worse in only the small percentage of cases in which the hair is too much not only where it should not be but also where it should be can the physician save his ego by asserting with any degree of confidence that the condition is not endocrinologic The only treatment he can offer is sympto matic which in this instance means the removal of the excess hair The Wonder stoen helps in some patients but most end up by turning to the painful costly and not too successful method of electroly sis For psychological reasons the physician must never mention the words beard or razor or *anything* which suggests mas culinity It is probable that the best way to remove the hair is with a razor What *is needed more than any other one thing* is a razor in disguise *e g* an electric razor that has been camouflaged with some fancy embellishment and called an elec tric depilator "

"Practical' versus "Theoretical" Knowl edge The subject matter of this paragraph is applicable to all internal medicine but especially to endocrinology The author is frequently asked in giving a talk to make it "practical and not too theoretical" By practical is usually meant therapeutic by theoretical is usually meant "funda mental The author has no patience with such a philosophy One cannot possibly practice good medicine and not understand the fundamentals underlying therapy Few if any rules for therapy are more than 90 per cent correct If one does not under stand the fundamentals one does more harm in the 10 per cent of instances to which the rules do not apply than one does good in the 90 per cent to which they do apply The same policy carries over to medical education There are those who advocate medical schools which will turn out practical physicians rather than theo rists But they end by turning out a poorer grade of doctors As with eggs there is no such thing as a poor doctor doctors are either good or bad

FULLER ALBRIGHT

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15 and 50 per cent of an administered dose of I^{131} within twenty four hours The maximal uptake is not reached until after twelve hours Values above 55 to 60 per cent are seen in patients with thyrotoxicosis patients with prolonged iodine deficiency those who have recently stopped a prolonged period of medication with one of the antithyroid drugs and in certain rare cases in which metabolic anomalies in hormonogenesis result in a hyperplastic gland with a high avidity for iodine Rarely patients with unusually active glands turn iodine over so rapidly that the peak accumulation has been passed by twenty four hours

Thyroid I^{131} uptake values below 15 per cent occur in hypothyroid states Abnormally depressed values are also seen in patients who are receiving antithyroid drugs or who have been receiving medications containing iodide or thyroid preparations The depressing effect on I^{131} uptake caused by iodide ingestion may not be relieved until many weeks after withdrawal in patients with normal thyroids but a high uptake may reappear in the thyrotoxic patient within a week after withdrawal The depressed uptake may persist for several weeks after the iodide is stopped

The rate of appearance of protein bound radioactive iodine in the serum after administration of a tracer dose also is used as an index of thyroid function The result may be expressed either as the fraction of the dose per liter of serum or as the ratio of protein bound I^{131} to total I^{131} expressed as per cent The latter is called the conversion ratio The test has certain theoretical as well as practical disadvantages but in general is a reliable index It may be abnormally elevated in patients who have undergone thyroidectomy or radioactive iodine treatment in the past

Other Tests of Thyroid Function The serum cholesterol is usually low in patients with thyrotoxicosis and high in patients with hypothyroidism There is a wide normal range in the measurement itself and there is considerable error

Since patients with certain types of hyperthyroidism may respond dramatically to administration of therapeutic doses of iodides this device has been used as a therapeutic diagnostic test Too often however an equivocal result is obtained and other tests are made less reliable by the administration of iodides The observation that thyroid function in patients with hyperthyroidism and diffuse hyperplasia of their glands (Graves disease) cannot be easily suppressed by administration of thyroxine or triiodothyronine has provided the thyroid suppression test Thus if administration of 150 micrograms daily of triiodothyronine for a week fails to suppress I^{131} uptake one concludes that the patient has Graves disease This test is having an increasing vogue and appears to be reliable and helpful in differentiating patients with mild thyrotoxicosis from normal subjects

Other tests may be of value in special circumstances The responsiveness of the thyroid to thyrotropic hormone may help in the differentiation of athyreotic and pituitary myxedema Thus a rise from low levels in I^{131} uptake and in serum concentration of protein bound iodine after a few injections of thyrotropin may indicate that the pituitary rather than the thyroid itself is at fault Since patients with Hashimoto s thyroiditis may have circulating antibodies to thyroglobulin precipitation and complement fixation tests may have diagnostic value in this disease The cephalin flocculation test may also be positive and diagnostically helpful in Hashimoto s thyroiditis More specialized tests are employed in the diagnosis of certain rare cases of metabolic cretinism For example it may be of interest to test the iodine binding capacity of the thyroid of such a patient by observing whether radioiodine in the gland is discharged after an oral dose of thiocyanate or whether diiodotyrosine is normally degraded after intravenous administration These tests are not as yet routinely employed in the clinical laboratory

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served until two or more days after administration but the effect is maintained and only slowly lost after several days The response to triiodothyronine may occur within six hours after administration and by thirty six to forty eight hours the response has disappeared Thus the total response to the two drugs is about the same but that of triiodothyronine occurs more quickly and is initially greater There is controversial evidence to suggest that the acetic acid derivatives of thyroxine and triiodothyronine have a much more rapid metabolic effect The suggestion has been made therefore that thyroxine is initially degraded in order to exert its specific action

The growth and function of the thyroid is under the control of the thyrotropic *hormone secreted by the basophilic cells* of the anterior pituitary These cells in turn vary their secretion rate in response to the thyroid hormone concentration in the plasma Thus a fall in the plasma concentration of thyroid hormone is countered by an increased secretion of thyrotropin which stimulates the thyroid to increased production of hormone The pituitary is at least partly under hormonal control from centers in the hypothalamus

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TESTS OF THYROID FUNCTION

A wide variety of laboratory aids are available in the assessment of the functional state of the thyroid gland Since most of these tests measure different aspects of thyroid function it is usually advantageous to secure two or more tests when the diagnosis is in doubt

Basal Metabolic Rate When properly performed this is a simple and reliable index of the thyroid function It suffers the disadvantage that there is a wide normal range and that subjective factors may cause significant alterations in the readings In certain patients in whom the reliability of other tests has been obscured by medication the basal metabolic rate may provide the only guide to diagnosis or response to a therapeutic program In addition to patients with hyperthyroidism elevated readings may be seen in those with malignant lymphoma certain blood disorders pheochromocytoma asthma congestive heart failure and in fever There may be abnormally low values in Addison s disease and in malnutrition

Serum Protein Bound Iodine Measurement of the quantity of iodine which is precipitable with the plasma proteins is a generally reliable index of thyroid function but the chemical estimation is difficult The normal range is from 3 5 to 8 0 micrograms per 100 ml In addition *to thyrotoxicosis abnormally high values* may be seen after ingestion of large amounts of iodide and may persist for months after administration of iodinated substances used in the visualization of the gallbladder bronchial tree and spinal canal In patients with Hashimoto s thyroiditis and in other types of thyroiditis as well and also in patients shortly after administration of therapeutic doses of radioactive iodine elevations in the serum concentration of protein bound iodine may be observed but in contrast to normal much of this protein bound iodine is not extractable by acid butanol Abnormally low serum concentrations are observed in hypothyroid states and during the twenty four to forty eight hours after the administration of mercurial diuretics because of the interference of mercury with the chemical analysis

Tests Employing Radioactive Iodine Tests employing radioactive iodine are now widely available The most commonly used is the thyroidal uptake The technique varies among laboratories but usually the patient is given an oral dose of 10 to 20 μc of I^{131} in water and the fraction of this which accumulates in the neck is measured twenty four hours later Appropriate corrections must be made for radiation absorption and back scatter and for the particular geometrical system which is used Variations in *the test include measur*ing at six hours or at forty-eight hours plotting the accumulation by f equent measurements over the neck and assaying the amount of I^{131} which appears in the urine during the first two days after administration More elaborate tests provide a measure of the thyroid clearance rate Normally the thyroid accumulates between

Holland and in southern Ireland In the United States it is found in the Great Lakes area Minnesota Ohio and in the Pacific northwest

Experimentally certain foods such as soya bean and cabbage may block normal synthesis of thyriod hormones and thereby cause compensatory hyperplasia of the gland There is an unsubstantiated suspicion that these substances may play a role in the production or accentuation of endemic goiter It has been proved in a district of Tasmania that goiter of school children is related to ingestion of milk from cows fed on a species of kale Many other dietary and environmental factors have been suggested such as arsenic excessive calcium in the diet infection polluted water and so forth but there is no proof for any of these Proof of the validity and adequacy of the iodine deficiency theory has been the striking disappearance of endemic goiter in those areas where iodized salt has been introduced particularly in the United States and Switzerland

Symptoms Apart from gradual enlargement of the thyroid there may be few or no symptoms In the most severe endemic districts however patients with goiter may be lethargic and have retarded skeletal development and deafness In such areas endemic cretinism makes its appearance As the gland enlarges there may be laryngeal stridor on exertion and difficulty in swallowing Rarely paralysis of a recurrent laryngeal nerve occurs

When the endemic is mild the disease is confined to adolescent females who have small diffusely enlarged glands and to older women with small nodular goiters When deficiency of iodine is more severe goiter is seen also in males and at times in preadolescent children Physical findings except in severe cases are limited to the goiter in the neck This is diffusely enlarged in younger patients and becomes nodular as the disease progresses At times most or all of the goiter may lie substernally Only in the most severe cases are clinical signs of hypothyroidism evident The basal metabolic rate is usually normal but studies with radioactive iodine have demonstrated the avidity of these glands for the isotope Thus the standard uptake tests are in the abnormally high range Continued administration of large doses of iodides to these patients may lead to the appearance of hyperthyroidism (Jod Basedow)

The relationship of endemic goiter to malignant change in the thyroid is controversial The preponderant evidence seems to be that endemic goiter does not predispose to the development of cancer of the thyroid but this is a moot point

Prevention The use of iodized salt prophylactically was introduced by Marine and Kimball in 1917 in Akron Ohio Their remarkable studies were based on earlier investigations of Marine and have led to the world wide acceptance of iodide prophylaxis of this disease Techniques have varied with social and economic conditions In the United States salt is iodized to a concentration of one part in 10 000 whereas in Switzerland the salt is iodized to one part in 200 000 The World Health Organization recommends one part in 100 000 In other countries it has been found more convenient to administer iodides in candy once a week or several times a year More recently iodate has been used because of its greater stability in packages in humid areas It is just as effective as iodide The important fact is that goiter is prevented if it can be assured that the patient is receiving an average of at least 40 micrograms of iodide per day Thyroid hypertrophy results if the mean daily intake is less

Treatment Iodide is effective therapeutically only if it is administered shortly after the disease begins and before involutionary and cystic changes have occurred There is no advantage to giving more than approximately 5 mg per day since more than this is rejected by the thyroid Even when full daily doses of iodide are given regressive changes are slow in developing and there may be no effect until weeks or months have passed if ever Somewhat better results may be obtained by the administration of thyroid hormone in dosage of 0 1 to 0 3 mg daily Occasionally a goiter will be found to melt away dramatically if it is of recent origin

If treatment is necessary it will usually be found that surgical removal is required The surgical indications are increasing pressure symptoms and suspicion of malignant change Cosmetic reasons may also be sufficient warrant for surgical removal

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Simple Nonendemic Goiter

(*Colloid Goiter Simple Struma Adolescent Goiter*)

Definition Simple nonendemic goiter is defined as parenchymal hypertrophy of the thyroid which is not dependent upon dietary inadequacy of iodine

Etiology The cause or causes of this disease are largely unknown Because it is most often seen in adolescent females endocrine factors have been suggested but not proved Since constituents of certain foods especially of the cabbage family may cause goiter by specifically inhibiting hormone synthesis it has been thought that dietary factors might be responsible for some cases of sporadic goiter and this has been proved in a few instances Sometimes a familial incidence is recorded suggesting that genetically determined metabolic factors may play a role Indeed there is evidence in certain cases to indicate that genetically determined enzymatic activity in the thyroid is limited and that goiter has resulted as a compensatory phenomenon

Signs, Symptoms and Course The disease usually produces no symptoms except gradual enlargement of the thyroid Often the enlargement of the thyroid is noticed only during the adolescent years and gradually disappears as the patient becomes older but more often the disease gives way to nodular goiter in middle life and may progress to toxic nodular goiter in the sixth and seventh decades As it progresses over the years increasing nodularity and size *may cause pressure symptoms Malignant* degeneration may occur but the frequency is probably less than 2 per cent There are usually no symptoms or signs of hypothyroidism

Laboratory studies are not helpful The metabolism test is usually normal and measurement of radioactive iodine metabolism by these glands is usually within normal limits as is the determination of the serum concentration of protein bound iodine Blood cholesterol is normal Needle biopsy is often helpful in differentiating this disease from chronic thyroiditis with which it is frequently confused

Treatment Administration of iodide is of little or no value Some cases particularly early cases in young patients may respond dramatically to desiccated thyroid Whenever simple goiter is encountered in adolescents it is probably advisable to administer desiccated thyroid or thyroxine for several years until the growth stimulus whatever it may be has passed Thyroid hormone is usually of little value in treatment of simple goiter which has become nodular Nonendemic multinodular goiter generally requires no treatment unless the growth is causing pressure symptoms or unless recent growth of a focal area in the nodular mass suggests malignant change The nodular goiters of older patients tend to produce thyrotoxicosis Since this change is gradual and often unrecognized by the patients the principal manifestations may be reflected in the cardiovascular system Whenever cardiac arrhythmias congestive heart failure or osteoporosis occurs in patients with nodular goiter the suspicion of thyrotoxicosis must be entertained

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Endemic Goiter

Definition Endemic goiter can be said to *exist when a distinct enlargement of the* thyroid gland can be detected in more than 10 per cent of the population Since other kinds of thyroid disease may exist in an area where goiter is endemic a diagnosis of endemic goiter rests necessarily upon exclusion of other possibilities

Etiology and Occurrence Most authorities are now agreed that a deficiency of iodine in the soil and water is the principal cause of endemic goiter The possibility remains that genetic and other factors may accentuate the sensitivity of certain patients to iodide deficiency Endemic goiter is still found in the Alps—especially in the Austrian Tyrol—in the Himalayas the Pyrenees the Carpathians the entire Andean chain and in the mountains of New Zealand There are also endemic areas in central Africa southern central China and certain localized areas in Japan and Brazil Endemic goiter is also seen in Finland

tion is common There may be an increase in the frequency of bowel movements but diarrhea occurs only in advanced and severe cases Signs and symptoms of congestive heart failure may be observed in patients with severe thyrotoxicosis or long continued and neglected disease This is particularly true of those patients with toxic nodular goiter whose symptoms of failure of the circulation may bring them to the attention of the physician Usual doses of cardiac glycosides are often ineffective in completely controlling the heart rate and the congestive failure Emotional lability especially in females is more often present than not Menstrual flow is reduced in amount Insomnia contributes to the fatigue Patients with Graves disease occasionally mention that their eyes have become more prominent and at times complain of itching burning lacrimation and diplopia This latter group of symptoms suggests the presence of what has been called the ophthalmopathic type of Graves disease wherein the ocular symptoms dominate the clinical picture

The striking features of Graves disease may be recognized at first glance but more commonly than not the definitive physical findings must be sought in more subtle manifestations Prominence of the eyes may be seen and the proptosis of the optic bulb can be measured Signs of sympathicotonia include lid lag globe lag diminished blinking and retraction of the upper and sometimes of the lower eyelid Occasional patients have weakness or complete paresis of the extraocular movements Patients with the advanced ophthalmopathic type of Graves disease may show the most menacing peribulbar edema proptosis chemosis conjunctivitis and diminution in visual acuity The skin is fine velvety warm and moist There is a fine rapid tremor of the extended fingers and tongue which must be distinguished from the coarser tremors of Parkinson s disease alcoholism and apprehension The hair is fine The thyroid may be scarcely enlarged or many times the normal size but it is always firmer than normal It rises with swallowing A bruit may be heard over the gland and a thrill palpated Rarely a toxic thyroid may be so low in the neck as not to be felt but a diagnosis of thyrotoxicosis in the absence of a palpable goiter is hazardous The pulse is quick and bounding the systolic blood pressure is increased and pulse pressure widened There may be a systolic scratch over the cardiac pulmonic area The rest of the physical examination is customarily normal except that occasionally patients with the exophthalmopathic type of Graves disease show circumscribed erythematous thickenings over the anterior surfaces of their shins and rarely over the dorsa of their fingers and hands Weakness of the skeletal muscles may occasionally be so severe as to be easily demonstrated Lymphoid hyperplasia and splenic enlargement are sometimes seen Younger patients with Graves disease usually show no evidence of congestive heart failure and the cardiac rhythm is usually normal In more severe cases and in patients with underlying heart disease atrial fibrillation and flutter occur The circulation is rapid the failure of the circulation being of the "high output type Older patients with toxic nodular goiter may also show the characteristic findings of congestive heart failure with enlargement of the heart various arrhythmias and fluid accumulation Angina pectoris is not a common cardiac manifestation of thyrotoxicosis

Patients with long-continued and severe thyrotoxicosis may enter a phase of the disease which has been termed thyroid crisis or storm This is most often precipitated by trauma especially in the neck



FIG 72 Typical Graves disease in a thirty year old woman Note the goiter and the widened palpebral fissures

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Hyperthyroidism

(Thyrotoxicosis Toxic Goiter Exophthalmic Goiter Graves Disease Basedow s Disease)

Definition Hyperthyroidism may be defined as the constellation of signs and symptoms which arises when there is an excessive concentration of thyroid hormones in the blood It may result from excessive administration of thyroid hormone (thyrotoxicosis factitia) from diffuse hyperplasia and hypertrophy of the thyroid (parenchymatous toxic goiter Graves disease Basedow s disease) or from an overproduction of thyroid hormones by the autonomous nodules of toxic nodular goiter All forms of hyperthyroidism are marked by an increased rate of tissue oxidation and by certain disturbances of the neuromuscular systems In addition in Graves disease *certain characteristic ocular abnormalities* may be observed

Etiology and Pathogenesis The cause of Graves disease has escaped detection Many of the anatomical and functional changes which are observed in this malady can be reproduced in animals by administration of the thyrotropic hormone from the anterior pituitary These observations have suggested that Graves disease can be traced to overactivity of the pituitary gland and in turn perhaps to stimulation from higher centers by way of the hypothalamus Nevertheless measurements by the most sensitive methods have usually failed to disclose an increased concentration of thyrotropic hormone in the blood of these patients Further the thyrotropic hormone in its purest form fails to cause the ocular manifestations which are characteristic of the human disease A closely associated factor from the pituitary has been found which causes proptosis of the eye of the Atlantic sea minnow without stimulating the thyroid

There is support from the clinic for the neurogenic theories of the origin of Graves disease Often patients with this disorder relate the beginning of their symptoms to major emotional or traumatic crises in their lives It has yet to be proved that these factors are more than precipitating or indeed that they have been more than coincidental The striking familial incidence of Graves disease has suggested a constitutional or genetic factor There seems to be no support for toxic or infectious theories

With the exception of the ophthalmic findings all the signs and symptoms of Graves disease can be attributed to excessive secretion of thyroid hormones These include elevated basal metabolic rate increased sweating muscle wasting and weakness tremor increased bowel activity increased appetite rapid and irregular heart action weight loss and apprehensiveness The pathogenesis of the ocular manifestations and of the pretibial myxedema which sometimes accompanies them is even more obscure These latter changes result from the deposition of highly polymerized mucopolysaccharides in the ocular muscles and in the interstitial tissues of the orbit and in the skin

Patients with toxic nodular goiter do not develop ocular proptosis or periorbital swelling and edema but the signs of sympathicotonia such as lid lag and lid retraction may be observed All symptoms can be attributed to chronic excessive secretion of thyroid hormones

Clinical Picture Thyrotoxicosis may be seen in all grades of severity It may begin explosively but more commonly the symptoms develop so gradually that the patient is scarcely able to date the beginning accurately Physical or psychic trauma may initiate symptoms Perhaps the most common symptom of all is fatigue Quadriceps weakness may be particularly evident when the patient attempts to ascend or descend stairs Rapid heart action and irregular beating of the heart are commonly experienced More often than not there is an increase in appetite and at times this may be a pronounced symptom Often satiety is quickly reached Weight loss occurs in spite of increased food intake In older patients and rarely in younger patients the appetite may be poor Sometimes it may be so stimulated that an actual weight gain is recorded There may be a fine tremor of the fingers and less often the patient complains of feeling tremulous all over The handwriting may deteriorate Most patients are intolerant of heat but close questioning may be necessary to elicit this fact with certainty Excessive sweating is characteristic and at times itching of the skin occurs Shortness of breath on exer

tion is common There may be an increase in the frequency of bowel movements but diarrhea occurs only in advanced and severe cases Signs and symptoms of congestive heart failure may be observed in patients with severe thyrotoxicosis or long continued and neglected disease This is particularly true of those patients with toxic nodular goiter whose symptoms of failure of the circulation may bring them to the attention of the physician Usual doses of cardiac glycosides are often ineffective in completely controlling the heart rate and the congestive failure Emotional lability especially in females is more often present than not Menstrual flow is reduced in amount Insomnia contributes to the fatigue Patients with Graves disease occasionally mention that their eyes have become more prominent and at times complain of itching burning lacrimation and diplopia This latter group of symptoms suggests the presence of what has been called the ophthalmopathic type of Graves disease wherein the ocular symptoms dominate the clinical picture

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Fig 72 Typical Graves disease in a thirty year old woman Note the goiter and the widened palpebral fissures

region as following thyroid surgery in an inadequately prepared patient Classically thyroid storm is a sudden and severe accentuation of all the typical findings in the disease There are great restlessness delirium high fever rapid tachycardia with arrhythmias sweating shock persistent vomiting and dehydration The mortality in patients with thyroid storm may exceed 66 per cent During recent years more adequate treatment of thyrotoxic patients better recognition and particularly better preoperative preparation have made this long dreaded complication a rarity Most rarely of all patients may enter a stage of exhaustion which has been termed apathetic thyroid storm This is characterized by apathy extreme muscle weakness disorientation rapid tachycardia collapse shock and sometimes gastrointestinal hemorrhage

Laboratory Examinations Typically the basal metabolic rate is elevated in patients with thyrotoxicosis and the degree of elevation correlates with the severity of the disease A wide range of normal values makes it possible for an occasional patient to have thyrotoxicosis and a basal metabolic rate which is in the upper limits of the normal range The protein bound iodine concentration of the serum is elevated above 8 0 micrograms per 100 ml and returns to normal as the disease is treated The degree of elevation forms only a rough guide to the severity of the disease

The uptake of radioactive iodine by the hyperplastic gland is usually increased above 60 per cent The absolute value of the uptake is not a reliable index of the severity of the disease Occasional patients with small hyperfunctioning thyriod glands will turn over the radioactive iodine so rapidly that a normal or low normal twenty four hour radioiodine uptake test may be obtained Measurement over the thyroid within the first few hours following administration or measurement of the quantity of protein bound radioactive iodine in the blood will obviate this error

In thyrotoxicosis there is a depression in the serum concentration of cholesterol Slight glycosuria and hyperglycemia may result from an increased rate of absorption of glucose from the gut There may be negative nitrogen calcium and phosphorus balances and these may lead to severe demineralization in the bones in severe cases of long duration

Diagnosis Usually a diagnosis of thyrotoxicosis causes no particular difficulty The symptoms of heat intolerance weight loss excessive appetite and muscular weakness suggest the diagnosis which is confirmed by tachycardia warm moist skin hyperexcitability widened pulse pressure and often ocular manifestations The diagnosis is confirmed by the usual laboratory findings of elevated basal metabolic rate increased uptake of radioactive iodine and an elevated serum concentration of protein bound iodine There may be no ocular findings Occasionally the patients present themselves with only or predominantly the symptoms and signs of congestive heart failure This is particularly true in those of the older age group who have had nodular goiter for a number of years and in whom the slow progress of thyrotoxicosis is so subtle that damage to an aging heart has occurred before the other symptoms of thyrotoxicosis have come to the patient s attention

Thyrotoxicosis should rarely be confused with other conditions Anxiety states may mimic the hyperexcitability and the palpitations tachycardia and tremor of neurocirculatory asthenia may resemble those of hyperthyroidism However the skin is cool and damp the tachycardia disappears during sleep and the tremor is coarse rather than fine The basal metabolic rate and other tests of thyroid function are within normal limits Occasionally the symptoms of chronic alcoholism resemble those of thyrotoxicosis but the tremor is coarse and the laboratory data are normal except the basal metabolic rate which may be modestly elevated Patients with pulmonary emphysema and fibrosis and with bronchial asthma sometimes show prominence of the eyes and may bear a superficial resemblance to patients with thyrotoxicosis in other ways such as weight loss tachycardia shortness of breath and sweating Patients with Parkinson s disease may sweat excessively and may be intolerant of the heat but here the resemblance ends Tachycardia and an elevated basal metabolic rate are seen in pheochromocytoma

Although in the last analysis the diagnosis depends upon confirmatory laboratory data these tests may be misleading The use of iodide and iodinated dyes of all descriptions intereferes with the radioactive iodide test and with the determination of the protein bound iodine in the blood Mercurial diuretics also interfere with the determination of the protein bound iodine Recent medication with antithyroid drugs makes difficult the interpretation of all tests of thyroid function

Often the best course in confusing cases

is to withdraw all medication and to observe the patient closely over the succeeding weeks until the clinical and laboratory information becomes coherent It seems safe to say that if the diagnosis is questionable there is seldom any danger to permitting withdrawal of all medication provided that the patient is kept under close observation

In certain cases it may seem expedient to attempt a therapeutic diagnostic trial either with iodide or with an antithyroid drug In rare cases the response may be sufficiently dramatic to establish the diagnosis with certainty but more commonly than not the use of this technique in diagnosis leads to confusing or uninterpretable laboratory data and to an unconvincing clinical result Modern tools of laboratory investigation almost invariably provide a diagnosis except in those cases which have been previously confused by medication and then it is generally better to discard the medications and observe than to add to the confusion by another trial of medication

Clinical Course and Prognosis The course of thyrotoxicosis varies widely among patients In some the disease is explosive and leads within a few weeks to such profound changes that treatment is urgent More commonly the disease proceeds more leisurely with ups and downs and occasionally after several months or years may remit entirely but these patients are always subject to recurrences The prognosis for the untreated patient is not good The gradual attrition against the cardiovascular system may result in congestive heart failure after months or a few years but the heart is not usually damaged permanently unless thyrotoxicosis is superimposed on some other form of heart disease Malnutrition may pave the way for intercurrent infections

Intercurrent infections may not be well tolerated and are to be avoided in the thyrotoxic patient since occasionally they may precipitate thyrotoxic crises Generally the course of infections is more severe in the thyrotoxic patient and in turn accentuates the thyrotoxicosis Infectious hepatitis may be particularly severe in the thyrotoxic patient

The ophthalmopathic form of Graves disease presents a special problem This manifestation of thyrotoxicosis also may be cyclic in nature but commonly the symptoms gradually subside and the appearance of the eyes returns toward normal Occasionally the proptosis and inflammatory changes progress relentlessly to the point where surgical decompression of the orbit is necessary Usually with care the patient can be tided over the active phases of the disease to enter a chronic state of fibrosis of the orbital contents without active progression The patients may be left with proptosis and in some cases ophthalmoplegia

Treatment Thyrotoxicosis may be successfully treated by several methods These include surgical removal of the thyroid radioactive iodine and protracted medical therapy with the antithyroid drugs or iodide External irradiation of the thyroid gland has been largely abandoned but some patients can be successfully treated by this technique

Iodine as the exclusive therapeutic agent is seldom employed in the treatment of Graves disease The remission which may be achieved is usually incomplete and often unsustained More often the involuting effect of iodine is sought in the preparation of the patient for subtotal thyroidectomy In mild cases iodine may be used for ten days to two weeks as the sole preoperative preparative medication More commonly the patient is prepared by administration of an antithyroid drug such as propylthiouracil until nearly euthyroid and iodide is added in the last few days before surgery in order to cause involution and decreased vascularity of the gland Iodine is remarkably potent in producting its effect As little as 5 mg per day may be sufficient to in



Fig 73 Ophthalmopathic form of Graves disease in a thirty six year-old woman

region as following thyroid surgery in an inadequately prepared patient Classically thyroid storm is a sudden and severe accentuation of all the typical findings in the disease There are great restlessness delirium high fever rapid tachycardia with arrhythmias sweating shock persistent vomiting and dehydration The mortality in patients with thyroid storm may exceed 66 per cent During recent years more adequate treatment of thyrotoxic patients better recognition and particularly better preoperative preparation have made this long dreaded complication a rarity Most rarely of all patients may enter a stage of exhaustion which has been termed apathetic thyroid storm This is characterized by apathy extreme muscle weakness disorientation rapid tachycardia collapse shock and sometimes gastrointestinal hemorrhage

Laboratory Examinations Typically the basal metabolic rate is elevated in patients with thyrotoxicosis and the degree of elevation correlates with the severity of the disease A wide range of normal values makes it possible for an occasional patient to have thyrotoxicosis and a basal metabolic rate which is in the upper limits of the normal range The protein bound iodine concentration of the serum is elevated above 8 0 micrograms per 100 ml and returns to normal as the disease is treated The degree of elevation forms only a rough guide to the severity of the disease

The uptake of radioactive iodine by the hyperplastic gland is usually increased above 60 per cent The absolute value of the uptake is not a reliable index of the severity of the disease Occasional patients with small hyperfunctioning thyriod glands will turn over the radioactive iodine so rapidly that a normal or low normal twenty four hour radioiodine uptake test may be obtained Measurement over the thyroid within the first few hours following administration or measurement of the quantity of protein bound radioactive iodine in the blood will obviate this error

In thyrotoxicosis there is a depression in the serum concentration of cholesterol Slight glycosuria and hyperglycemia may result from an increased rate of absorption of glucose from the gut There may be negative nitrogen calcium and phosphorus balances and these may lead to severe demineralization in the bones in severe cases of long duration

Diagnosis Usually a diagnosis of thyrotoxicosis causes no particular difficulty The symptoms of heat intolerance weight loss excessive appetite and muscular weakness suggest the diagnosis which is confirmed by tachycardia warm moist skin hyperexcitability widened pulse pressure and often ocular manifestations The diagnosis is confirmed by the usual laboratory findings of elevated basal metabolic rate increased uptake of radioactive iodine and an elevated serum concentration of protein bound iodine There may be no ocular findings Occasionally the patients present themselves with only or predominantly the symptoms and signs of congestive heart failure This is particularly true in those of the older age group who have had nodular goiter for a number of years and in whom the slow progress of thyrotoxicosis is so subtle that damage to an aging heart has occurred before the other symptoms of thyrotoxicosis have come to the patient s attention

Thyrotoxicosis should rarely be confused with other conditions Anxiety states may mimic the hyperexcitability and the palpitations tachycardia and tremor of neurocirculatory asthenia may resemble those of hyperthyroidism However the skin is cool and damp the tachycardia disappears during sleep and the tremor is coarse rather than fine The basal metabolic rate and other tests of thyroid function are within normal limits Occasionally the symptoms of chronic alcoholism resemble those of thyrotoxicosis but the tremor is coarse and the laboratory data are normal except the basal metabolic rate which may be modestly elevated Patients with pulmonary emphysema and fibrosis and with bronchial asthma sometimes show prominence of the eyes and may bear a superficial resemblance to patients with thyrotoxicosis in other ways such as weight loss tachycardia shortness of breath and sweating Patients with Parkinson s disease may sweat excessively and may be intolerant of the heat but here the resemblance ends Tachycardia and an elevated basal metabolic rate are seen in pheochromocytoma

Although in the last analysis the diagnosis depends upon confirmatory laboratory data these tests may be misleading The use of iodide and iodinated dyes of all descriptions intereferes with the radioactive iodide test and with the determination of the protein bound iodine in the blood Mercurial diuretics also interfere with the determination of the protein bound iodine Recent medication with antithyroid drugs makes difficult the interpretation of all tests of thyroid function

Often the best course in confusing cases

recurrence is extremely rare Depression of the bone marrow and malignant change in the thyroid have not been observed nor have untoward effects on the germ plasm been observed In spite of the absence of these effects but in view of the hypothetical risk of radiation carcinogenesis it is still customary in most clinics to limit radio iodine therapy to patients beyond the age of forty Younger patients are treated sur gically unless there are specific contraindi cations For example radioiodine is used in younger patients who have complicating heart disease or who have had thyroid surgery in the past and in whom repeated surgery might carry an added operative hazard

Radioiodine has been most widely used in the treatment of Graves disease It can also be used successfully in the therapy of toxic nodular goiter but the results are less satisfactory Usually larger doses are necessary and failure of the initial dose to be effective is more common

The outstanding complication of radio iodine therapy is myxedema This has oc curred in 10 to 20 per cent of treated pa tients Hyperthyroidism is temporary in some patients and if desiccated thyroid is withheld the patient will return to nor mal after a few weeks Usually however it will be necessary to treat indefinitely with 0 1 to 0 2 gm of desiccated thyroid

Thyroidectomy is an effective way of treating thyrotoxicosis in the suitably pre pared patient Because of the availability of the antithyroid drugs there is now no excuse for a surgical approach to a thyro toxic patient until the hyperthyroidism has been controlled Without control surgery of the hyperfunctioning gland is accom panied by a high incidence of thyroid crisis

At surgery approximately 2 to 3 gm of thyroid tissue are usually left in each side of the neck The hyperplasia which these remnants undergo in the postopera tive phase is usually sufficient to provide enough thyroid hormone for the patient The frequency of postoperative myxedema depends in large part upon the amount of thyroid tissue which is left Most series have recorded an incidence of 5 to 10 per cent Within a five year period approxi mately 5 to 10 per cent of patients operated upon can be expected to show a recur rence of their disease The recurrence rate is doubtless dependent upon the extent of the subtotal thyroidectomy In order to prevent recurrence some surgeons perform a radical thyroidectomy with the expecta tion that the patient will require desic cated thyroid for the remainder of his life

Damage to a single recurrent nerve is not a serious complication of thyroid sur gery and is often temporary It results in hoarseness and in inability to produce a sharp cough It is always well to examine the vocal cords both before and after op eration If both nerves are severed an immediate and permanent tracheotomy is usually required Serious postoperative in fection or hemorrhage is not often en countered

The parathyroid glands are often tem porarily damaged during surgery Symp toms of tingling and tightness in the fingers and a positive Chvostek sign may appear within eight hours Mental depression and anxiety are common symptoms Calcium lactate 1 0 gm every four hours orally may be sufficient to control the hypocal cemia or it may be necessary to provide calcium intravenously and to give up to 50 000 or more units of vitamin D daily Dihydrotachysterol (AT 10) has little if any therapeutic advantage over vitamin D The parathyroids are permanently dam aged only rarely

The choice of therapy in thyrotoxicosis depends upon the problems which the pa tient presents and the resources which are available Once the diagnosis has been established one can proceed cautiously toward the institution of the therapy of election Radioiodine is indicated for pa tients with diffuse hyperplasia of the thy roid in the age group beyond forty This includes perhaps two thirds of all thyro toxic patients No preparation is needed unless the functional state of the thyroid has been altered by previous medication and in most cases the patient can be treated on an ambulatory basis Only when the disease is advanced or when there are cardiac or other complications will hos pitalization be required Radioiodine will also be customarily the therapy of choice in younger patients with complicating heart or other diseases when surgery seems un desirable In most clinics at the present time younger patients who have no sur gical contraindications are prepared as pre viously stated

Therapy of thyrotoxicosis by continuous administration of the antithyroid drugs is less effective because of the difficulty in maintaining precise control and the high recurrence rate after cessation of the drug Patients who are treated in this way must be followed closely on the program for a year or two If there is inadequate control or if recurrence is observed following cessa

duce a full therapeutic remission Customarily five drops of a saturated solution of potassium iodide are used twice daily Medication with larger amounts gives no increased effect The fall of the basal metabolic rate takes place at the same rate upon administration of iodide as after withdrawal of desiccated thyroid from a patient treated for myxedema For this reason it is thought that iodine somehow prevents release of hormones from the gland by inhibiting the effect of thyrotropin The problem of why iodide causes the return of the thyrotoxic patient to normal or nearly normal but fails to cause hypothyroidism has not been solved Rarely the use of iodine results in myxedema and this usually is accompanied by growth of a large goiter

Thiourea and its derivatives are effective therapeutic agents in the treatment of thyrotoxicosis Since these drugs do not prevent the release of preformed hormone their effectiveness is not as rapid as that of iodide Usually within two to three weeks after beginning therapy the patient experiences a gradual amelioration of symptoms such as tachycardia tremor and heat intolerance and an increased sense of well being and strength Patients with small glands may be completely freed of symptoms of thyrotoxicosis within six to eight weeks and rarely even sooner whereas patients with large glands with much stored hormone may require the use of these drugs for eight to twelve weeks or more before achieving a remission The effectiveness of these drugs in blocking the utilization of iodine in the thyroid is limited to a few hours Accordingly for maximum effectiveness it is necessary that they be given every six to eight hours

The antithyroid drugs may be used either in preparation for surgical removal of the gland or continuously for medical control of the disease If thyroidectomy is the goal the antithyroid drug is used until the basal metabolic rate is normal and the patient has begun to gain weight The drug is continued and in addition the patient is given five drops of a saturated solution of potassium iodide daily for five or six days before operation If he is to be treated continuously with medication full doses are given until the patient is clinically euthyroid and then the dose is gradually reduced and the frequency of medication lessened In this way treatment may be continued for six months to a year or longer and then withdrawn All observers are agreed that approximately one half to two thirds of all patients who are treated in this way have a recurrence within a few weeks to months after the medication is withdrawn If this occurs the antithyroid drug can be reinstituted or a different and more definitive plan of therapy undertaken Rarely patients develop hypersensitivity to the antithyroid drugs of the thiourea group There may be minor rashes but more serious complications such as granulocytopenia and febrile responses occur in about 1 per cent of the cases and jaundice has been reported In the event of a reaction of hypersensitivity another of the antithyroid drugs may be tried since cross sensitivity is not common For patients who require antithyroid medication and who cannot tolerate the drugs of the thiourea group potassium perchlorate is a potent antithyroid substance This may be used orally in doses of 300 mg every eight hours until the disease is controlled The effect of perchlorate is lost if iodides are given

Several members of the thiourea group are in common clinical use These include propylthiouracil which is customarily given in doses of 100 mg every eight hours methylthiouracil in the same dosage and 1 methyl 2 mercaptoimidazole in doses of 10 to 15 mg every eight hours

Radioactive iodine was introduced in the therapy of Graves disease in 1942 Initially a short lived isotope was employed but since 1946 I^{131} with a half life of eight days has been almost universally employed The simplicity of the technique and the excellence of the results have been so outstanding that it has become the preferred form of therapy The effectiveness of the isotope is due to its preferential location in the thyroid and to its beta ray emission which profoundly alters the function of thyroid parenchymal cells The degree of damage of a given dose is dependent upon the size of the dose the uptake by the gland the rate of turnover of the isotope the radiation sensitivity of the cells and perhaps to other factors Since few of these can be assessed with accuracy the dosage is empiric It has been found that excellent results can be obtained if the patient is given approximately 0 16 millicuries of I^{131} per gm of estimated thyroid weight This plan will result in permanent remission after a single dose in approximately 75 per cent of patients The remaining patients require a second and sometimes a third therapeutic dose A repeat dose is not usually given until an interval of several months has made it evident that the initial dose was inadequate to control the disease Once remission has been achieved

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tion of treatment it is wisest to resort either to radioiodine or to surgical removal of the gland

In only an occasional case is there sufficient muscle weakness or evidence of cardiac dysfunction to warrant bed rest Better therapeutic results will be achieved during the active phases of the disease if activity is limited to a degree which does not result in fatigue Insofar as possible emotionally disturbing factors should be removed from the environment Digitalis is used if there is auricular fibrillation or congestive heart failure but doses somewhat larger than those usually employed will be required Sedatives are often helpful A well balanced high caloric diet is required Vitamin supplements especially of the B group are prescribed in severe cases

The ophthalmopathic form of Graves disease presents special problems The progress of the ocular findings is not necessarily related to the state or change of the thyrotoxic elements of the disease Thus progressive ophthalmopathy may occur in thyrotoxic as well as in hypothyroid patients and remissions are seen both as the patient becomes more thyrotoxic and as hypothyroidism is induced therapeutically Hypothyroidism is to be avoided in patients with progressive ophthalmopathy Thyrotoxicosis if present should be treated The eyes should be protected by suitable glasses against bright sunlight and against dust and wind Often it will prove helpful to have the patient sleep in a semi sitting position The inflammation and chemosis which mark a more severe case may be treated with a collyrium of hydrocortisone Intensive diuretic therapy is of value in severe cases Relentless proptosis with ulceration or threatened ulceration of the cornea and progressive loss of visual acuity are the usual indications for surgical decompression of the orbits Roentgen therapy to the orbits the pterygoid fossa or the pituitary is disappointing Results are slow and may be no more than are seen in the natural fluctuations of the disease There is no specific therapy for the ophthalmoplegia On the theory that the ophthalmic syndrome is dependent upon a pituitary factor which can be suppressed by desiccated thyroid administration of this medication is advisable

Thyrotoxic crisis is a major medical emergency Bed rest and adequate sedation are essential The patient should be treated with oxygen and if his temperature is dangerously elevated with ice bags or alcohol sponges Maximal control of the thyrotoxicosis is achieved by full doses of an antithyroid drug such as 1 methyl 2 mercaptoimidazole followed in a few hours by full doses of iodides These medications can be given orally or parenterally if the patient is vomiting Shock and dehydration are treated by parenteral replacement therapy with blood and balanced salt solutions Any suspicion of infection requires use of antibiotic medications Since adrenal failure may play some role in thyrotoxic crisis the patient should be supported with cortisone or prednisone He should be digitalized in an endeavor to control the ventricular rate in the event of auricular fibrillation or congestive failure The recent report that Rauwolfia alleviates certain peripheral manifestations of thyrotoxicosis including tachycardia suggests that a member of this group of drugs might be of value

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Thyroiditis

A number of pathological conditions of the thyroid gland have been grouped under the term thyroiditis Thyroiditis may be classified as acute suppurative acute non suppurative subacute and chronic Chronic thyroiditis is subdivided into Hashimoto s thyroiditis and Riedel s struma In addition the thyroid may be involved by tuberculosis syphilis and sarcoid

Acute suppurative thyroiditis is encountered with the greatest rarity either as a result of blood borne infection with the ordinary pyogenic organisms or by extension along the fascial planes of the neck from infection above It has been seen following infection or extraction of teeth

Acute thyroiditis is an inflammatory condition of the thyroid characterized by suddenness of onset It frequently follows a mild upper respiratory infection Some cases are thought to be caused by the virus of mumps The disease may be asymptomatic except for a swelling of the thyroid but more commonly it is associated with exquisite tenderness of the gland rapidly enlarging goiter and accompanying systemic manifestations such as chills and fever The radioactive iodine uptake test may be depressed to zero and there may be a transient elevation of the serum concentration of protein bound iodine Analysis of the organic iodine of the blood may indicate that it is thyroglobulin rather than thyroxine Antibodies against the patient s own thyroglobulin may make their appearance during the course of the disease The erythrocyte sedimentation rate is elevated for many weeks The disease follows an unpredictable course It may last for only a few days or may extend over weeks and may recur one or several times only to subside again Each exacerbation is usually less severe than the previous one The disease may involve the entire gland but occasional focal areas may be involved first on one side and then on the other Pathologically there is a focal or generalized inflammatory reaction replacing and destroying the parenchyma Suppuration does not occur The diagnosis is made from the signs and symptoms but needle biopsy may be necessary to establish the diagnosis

Assessment of modes of therapy for so uncommon a disease has not led to agreement In most cases symptomatic treatment with aspirin ice bag and bed rest is all that is necessary A few hundred r of x ray therapy may produce remission in many cases Though thyrotropic hormone desiccated thyroid and antithyroid drugs have been advocated there appears to be little rationale for their use Cortisone 100 to 200 mg daily suppresses the inflammation and almost invariably induces a subsidence of fever and evidence of inflammatory reaction However the symptoms and signs often recur as soon as cortisone is withdrawn The prognosis is good except only that some of these patients develop hypothyroidism and require thyroid hormone for maintenance thereafter

Subacute or pseudotuberculous thyroiditis is a less well defined and less commonly encountered inflammatory disease of the thyroid which is characterized by protracted course minimal to moderate symptoms and little fever or malaise Pathologically there are destruction of the parenchymal epithelium and infiltration of the thyroid substance with an inflammatory exudate containing giant cells This disease may be a variant of acute thyroiditis Its etiology remains unknown

Struma lymphomatosa described first by Hashimoto in 1912 is a chronic disease of the thyroid manifested clinically by progressive goiter with or without pressure symptoms Pathologically a characteristic lymphocytic infiltration replacement of the thyroid parenchyma occurs Recently it was shown that the patients have developed a sensitivity to their own thyroglobulin Thus the lymphocytic infiltration into the thyroid is thought to represent the tissue reaction to an antibody antigen reaction proceeding within the thyroid itself Just what initiates the process has not been made clear

The disease is much more commonly seen in females Usually they seek medical attention because of a mass in the neck or because of pressure symptoms Clinically there are no abnormal findings except for the mass in the neck and evidence of hypothyroidism The thyroid has a distinctive firm lobular configuration It is not tender Almost always there is thickening of the pyramidal lobe Usually the standard tests of thyroid function are within normal limits On occasion the radioactive iodine uptake and turnover may be slightly elevated Analysis of the protein bound iodine of the serum often discloses that a significant fraction is thyroglobulin Positive cephalin flocculation and colloidal gold tests may be obtained and a slight elevation in the serum gamma globulin concentration may be present

There is usually a slowly progressive enlargement of the gland until symptoms may require its removal Late in the disease there may be distinct evidence of hypothyroidism Surgical treatment of Hashimoto s thyroiditis is unnecessary unless there are pressure symptoms or the goiter is cosmetically unacceptable Early cases may respond to full doses of desiccated thyroid

Perhaps the rarest form of thyroiditis is *Riedel s struma* or ligneus thyroiditis It is always seen in older patients It develops insidiously and manifests itself primarily by pressure symptoms Pathologically there is dense fibrosis and infiltration into the neighboring structures in the neck The cause is unknown Some observers think that it represents an end result of Hashimoto s thyroiditis but most authorities do not agree The only known treatment is surgical removal

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Thyroid Nodules and Malignant Disease of the Thyroid

Nodules in the thyroid always raise the question of cancer When the gland is multinodular the problem is relatively simple because only a small fraction perhaps less than 2 per cent of these glands will show pathological evidence of malignant change When there is history of recent growth of one of the nodules when one of them appears particularly firm or when there is satellite adenopathy one should suspect malignant disease

Most pathologists are agreed that between 8 and 20 per cent of all single thyroid nodules are malignant *Some however question the pathological criteria which* have been applied They point to the low incidence of metastatic cancer of the thyroid as evidence against the malignant nature of single nodules Metastatic malignant disease from the thyroid is indeed rare but perhaps not so rare as statistics would indicate because of the chronic and relatively benign nature of metastatic thyroid malignant neoplasms

There is no reliable method short of surgical removal for distinguishing between benign and malignant thyroid tumors The nodule which is thought to be solitary clinically is often found at exploration to be a cluster of adenomas or cysts Most commonly the solitary nodule is composed of many small and large follicles with flattened epithelium and filled with colloid Sometimes pa[illegible] infoldings predominate and the [illegible] is called a papillary adenom[illegible] [illegible]-adenomas the histological structure of which resembles fetal thyroid may be transition forms to frankly malignant neoplasms

Carcinoma of the thyroid takes many different pathological forms and at times a variety of histological types are found in adjacent areas of the same tumor The most common tumor is the papillary carcinoma This is a slowly growing neoplasm which metastasizes first to the regional *nodes in the neck and only later to the* lungs bones and elsewhere It is a more *malignant and lethal disease in older* patients Treatment is surgical excision of the local lesion together with removal of the regional lymph nodes if they are suspected of being involved Localized distant metastases may be removed if technically feasible Pulmonary metastases from papillary carcinoma unlike the disease in the neck may be particularly susceptible to radiation therapy

The so called *benign metastasizing struma* is not a benign disease but a slowly growing follicular carcinoma of the thyroid There is always a primary lesion in the gland itself which satisfies the usual criteria of malignant change upon careful search by the pathologist Most often the disease declares itself as a metastatic lesion in a distant bony structure such as the pelvis hip spine or skull The distant metastasis pathologically resembles normal thyroid tissue These metastases are removed when surgically feasible They are the tumors which have been shown to take up significant amounts of radioactive iodine and accordingly are the ones which *benefit from radioiodine therapy there are* case reports which record dramatic improvement in local symptoms The disease under any circumstances is extremely indolent After many months or more often after many years other more malignant and invasive metastases make their appearance

Solid adenocarcinoma of the thyroid is a much more lethal and rapidly progressive disease than the types already mentioned The disease may spread with considerable rapidity from the thyroid to distant sites such as liver lung and bone It may also be found in the regional nodes Surgical excision of the local lesion offers the best opportunity for cure Deep x ray therapy also directed to the neck may be of more value in this type of thyroid cancer than in others

The small cell carcinomas of the thyroid are usually extremely malignant often progressing to death within weeks or a few

months Temporary alleviation of the symptoms may be gained from x ray therapy but radioiodine has no role A rare case can be ablated surgically if the disease is found early enough

Other types of neoplasia within the thyroid are encountered with less frequency Hodgkin s lymphoma may be found and metastases from tumors of lung large bowel kidney and elsewhere have been seen as well as plasma cell myeloma Epidermoid cancer of the thyroid is particularly malignant although exceedingly rare

In general it can be said that surgery offers the only satisfactory therapy for cancer of the thyroid It is frequently possible to excise local and distant lesions repeatedly in the course of the more benign neoplasms Radioiodine has proved disappointing in that few patients if any are cured by it and the symptomatic relief which can be achieved is limited to a small fraction of the cases Furthermore the technique is laborious time-consuming and expensive and highly undesirable effects on the bone marrow have been encountered Finally it should be noted that hypothyroid states are undesirable in the management of thyroid cancer because some of these tumors are dependent upon the thyrotropic hormone for growth and are stimulated to increased growth rate when the normal inhibition of thyrotropin production is withdrawn

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Hypothyroidism

Definition Hypothyroidism is a functional state which results when there is insufficient circulating thyroid hormone It is a result of anatomical absence or functional insufficiency of the thyroid gland There is also a possibility that certain patients may respond inadequately to normal amounts of one or both of the thyroid hormones Hypothyroid patients may be classified as having cretinism juvenile myxedema adult myxedema and hypothyroidism without myxedema The clinical findings are determined by the duration and degree of thyroid failure and the time of life at which it occurs

Etiology Cretinism results from thyroid deficiency in fetal or early neonatal life The diagnosis requires that there be retarded development in the skeleton and central nervous system The changes may be permanent and irreversible or not depending upon how early the diagnosis is made and the amount of damage which has occurred by the time therapy is instituted Endemic cretinism is seen in areas of the world where endemic goiter is found and its prevalence roughly parallels the severity of the endemic It is the result of an inadequate supply of iodine during critical growth phases of intrauterine and postnatal life Although the placenta concentrates iodide the maternal thyroid made avid for iodide by iodide lack may take precedence over the placenta and over the developing fetus for whatever iodide is available Endemic cretinism accordingly occurs in families whose members already show evidence of iodine want

Sporadic cretinism is a rare condition which results from embryonal failure of the thyroid gland to develop Small islands of aberrant thyroid tissue may produce enough hormone during fetal life to forestall irreversible damage provided that therapy is begun early in postnatal life

Metabolic cretinism results from failure of thyroid hormone synthesis because of a biochemical abnormality in the production of hormone in the gland These patients are rare and the condition usually occurs as an heredofamilial disorder At least four distinct types have been described but the end result is the same in all viz hypothyroidism and goiter One type lacks the ability to oxidize iodide to iodine in the thyroid The thyroids of another group are unable to couple iodotyrosine residues together to form hormonal iodothyronines The patients belonging to a third type have a body wide lack of an enzymatic system which deiodiates iodotyrosine These hormone precursors are lost from the body in the urine A fourth group of metabolic cretins secrete an abnormal iodinated protein from their thyroids into the blood

Juvenile myxedema differs from cretinism in that there is no permanent retardation of mental development The disease begins in childhood it is not present at birth *In most cases it is attributable to* destruction of the thyroid gland during the early years by unknown causes but in some it is due to failure of functioning aberrant remnants to produce sufficient *thyroid hormone as growth progresses* Thus it is possible to demonstrate hyper functioning thyroid tissue in some of these subjects but the quantity of hormone in the peripheral blood is below normal

The cause of primary adult myxedema is usually not known except in those patients in whom the thyroid gland is destroyed surgically or by radioactive iodine There is evidence to suggest that in some *cases destruction of the gland is the result* of an autoimmune process similar to that which has been described in thyroiditis Occasionally adult myxedema is seen as the end result of chronic thyroiditis Usually *only a fibrous remnant is found in the neck* This may contain a few isolated islands of acinar tissue Occasionally the clinical picture of myxedema dominates the clinical findings in Sheehan s syndrome in which *thyroid failure is traceable to pituitary* destruction

Hypothyroidism without myxedema may occur when the thyroid is incompletely destroyed This occurs occasionally after *radioiodine therapy or surgical ablation of* the thyroid and occasionally in the course of thyroiditis Confirming laboratory data may include a subnormal serum concentration of protein bound iodine and at times an increased uptake of radioiodine with rapid turnover by the surviving remnants More often than not however by the term hypothyroidism without myxedema is meant a vague syndrome characterized by fatigue and other neurasthenic symptoms coupled with a low basal metabolic rate It seems most probable that this condition has nothing whatever to do with the thyroid It has also been suggested that certain patients are hypothyroid because of an inability to convert thyroxine into triiodothyronine in the peripheral tissues Evidence for the existence of this syndrome is incomplete

Signs and Symptoms *Cretinism* Typically the cretin is dwarfed and mentally retarded Among the signs *which may be observed as* early as four weeks after birth are failure to feed properly an enlarged and protruding tongue umbilical hernia thickening and drying of the skin hyporeflexia and torpor *If the* disease is recognized at this stage therapy may permit normal development in some cases but in others irreversible changes have already taken place Later the characteristic hoarseness of cry *the round face the* eyes set wide apart the dark hair the yellow scaly skin and constipation may suggest to the experienced observer the presence of cretinism There is delayed dentition Retarded bone age is *one of the characteristic features of the* disease Juvenile or adult cretins present an unmistakable appearance The hair is usually black There may or may not be retarded genital development They are char*acteristically phlegmatic and cheerful* Endemic cretins and cretins with metabolic cretinism are goitrous whereas sporadic cretins are athyreotic A sporadic cretin never shows evidence of thyroid function by *laboratory tests* whereas often *the endemic* cretin will show normal thyroid function by radioactive iodine uptake test and by measurement of the serum concentration of protein bound iodine These tests do not *necessarily reflect the condition which* existed in fetal life or early thereafter when the irreversible damage was done

Juvenile myxedema differs little from adult myxedema except for evidence of *retardation of bony growth The facies may* not show the characteristic features of established adult myxedma but these changes are apparent to a degree if looked for The hair is coarse the skin is dry and *often there is hyperkeratosis pilaris* The skin is sallow and slightly yellow Dentition may be delayed but the mentality is normal although cerebration may be slow These patients may sometimes be thin because of poor appetite but more commonly they are moderately obese

Adult myxedema exists in all degrees of severity depending upon the completeness and duration of thyroid failure The patient usually has few complaints These consist of intolerance to cold dryness of the skin constipation a tendency to put on weight dry hair and diminished vigor The facies is pathognomonic The hair is thin and coarse the eyebrows thin the skin cool dry scaly and thickened *and the face puffy* particularly around the eyes The tongue is large The pulse is slow and regular The blood pressure in younger patients is normal but may be permanently elevated in *older patients* The heart may be enlarged and there may be pericardial pleural or abdominal fluid Carotenemia gives the face a typical faintly yellow color The reflexes show a characteristic slowness of the relaxation phase The speech is slow and

coarse and mentation is retarded Usually these patients are jolly but occasionally they are depressed and at times frankly psychotic The circulation is slow as evidenced by the circulation time The menses tend to be excessive and prolonged and often the bleeding can be shown by endometrial biopsy to be from a proliferative rather than a secretory endometrium There may be a mild normochromic or macrocytic anemia Vague pains in the extremities and in the back are common and stiffness of the joints is a frequent complaint

The signs and symptoms of pituitary myxedema may be indistinguishable from those of athyreotic myxedema The skin tends to be thin and finely crinkled rather than thickened but it may be necessary to resort to laboratory tests in order to distinguish between these two conditions

Diagnosis Hypothyroid states should be readily recognizable by attention to symptoms and from the characteristic features and activity of the patient The basal metabolic rate is typically in the neighborhood of minus 40 per cent in patients with athyreotic myxedema It may be somewhat lower in patients with pituitary myxedema Radioactive iodine uptake is less than 10 per cent except in those patients with metabolic cretinism or endemic cretinism when it may be normal or high The concentration of protein bound iodine in the serum is low and indeed the diagnosis cannot be made with certainty without this finding The circulation time is slow The electrocardiogram shows low voltage and flattened T waves The cholesterol concentration in the serum is above 250 micrograms per 100 ml but may not be elevated in pituitary myxedema

It is essential that hypothyroidism be recognized in the infant if it is present for thyroid deficiency during early critical phases of growth results in permanent retardation of mental and skeletal development On the other hand it is important to guard against the overdiagnosis of hypothyroid states Obese adolescents tired middle aged women patients with menstrual irregularities and children who are not progressing well in school often receive a gratuitous diagnosis of hypothyroidism Administration of thyroid to these patients usually results in no significant clinical change Many otherwise normal people show basal metabolic rates which vary from minus 20 to minus 30 These patients are best classified as hypometabolic without hypothyroidism They respond transiently or not at all to thyroid The decision for treatment with desiccated thyroid should depend upon an accurately determined serum concentration of protein bound iodine

It may be difficult to distinguish athyreotic from pituitary myxedema The history and appearance of the patient may provide a clue Evidence of normally functioning adrenals and gonads excludes a diagnosis of pituitary myxedema as does a finding of significant amounts of follicle stimulating hormone in the urine of a postmenopausal

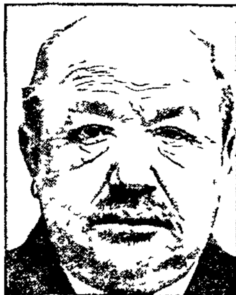




Fig 74 Typical athyreotic myxedema in a seventy five year-old man The photographs were taken before (upper) and after (lower) therapy (From Hertoghe E Practitioner 94 26 1915 By permission)

female To confuse the problem further it must be said that patients with athyreotic myxedema of long standing may rarely have inactive adrenals and pituitary It is sometimes of value to attempt to stimulate the thyroid with thyrotropic hormone measuring the change in serum protein bound iodine and I^{131} uptake *A positive response* indicates that the thyroid is inactive because of pituitary failure

Prevention and Treatment *Cretinism* Endemic cretinism can be prevented by the use of iodized salt or other prophylactic measures in the endemic areas Other kinds of cretinism cannot be prevented but many of the consequences can be prevented by early *recognition and vigorous treatment* The following table indicates the desiccated thyroid dose schedule for children

AGE	DAILY DOSAGE
2 to 4 months	6 mg
4 to 8 months	12 mg
8 to 12 months	18 mg
12 to 24 months	25–50 mg
2 to 4 years	30–100 mg
4 to 12 years	60–200 mg

A safe rule would seem to be to increase the dosage until the patient shows the earliest signs of thyrotoxicosis and to maintain dosage at just below this level increasing it as increase in size warrants a higher dosage The same program applies to athyreotic cretinism and to metabolic cretinism *Beneficial effects of treatment* should be apparent within a week The cretinous infant will show a decrease in weight thinning of the skin increased responsiveness and improved feeding Shortly thereafter renewed hair growth may be observed Treatment of established cretinism in the older child or in the adult is not successful Not only is there no evidence of improvement in mentation but desiccated thyroid often makes these patients irritable and more difficult to manage

Children with *juvenile myxedema* respond quickly to thyroid hormones with improvement in mood and mentation and renewed growth In some cases administration of full doses of thyroid has precipitated a psychotic reaction Withdrawal of the medication and reinstitution at a lower dose level gradually building up to an adequate one is sufficient to overcome this difficulty Patients with early *adult myxedema* should be given *full doses* of 0 1 to 0 2 gm of thyroid without delay If the patients are elderly or if there is heart disease or angina pectoris full doses of thyroid may increase the angina or precipitate fatal myocardial ischemia In older patients it will generally be found wisest to begin with doses of the order of 15 milligrams increasing by this amount each week until a full maintenance dose is reached

The changes in facies may be slow and full restoration of normal appearances may not be seen until several months have passed Patients generally report symptomatic improvement within a week and within three or four weeks they feel remarkably better Constipation is relieved they lose weight activity and energy improve and sensitivity to cold vanishes

Patients with pituitary myxedema must be treated with extreme caution since it has been shown that the adrenal insufficiency which these patients have is much accentuated when thyroid function returns to normal Full doses of thyroid given at once have precipitated Addisonian crisis in a few cases If the diagnosis is made the patient should be treated cautiously with *thyroid and in addition should receive sup*porting doses of adrenal cortical substance

At the present time there are few recognized occasions in which there is an advantage to be served by medication with triiodothyronine It is possible that a rare patient with extreme hypothyroidism of long standing and with congestive heart failure might be treated with this medication in a desperate effort if a few days delay in response might seem dangerous There appears to be no advantage to giving thyroxine rather than desiccated thyroid provided that a U S P preparation of the latter is employed

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DISEASES OF THE PARATHYROID GLANDS

Introduction Diseases of the parathyroid glands include primary hyperparathyroidism and hypoparathyroidism For clinical purposes the latter includes pseudohypoparathyroidism although there is evidence that this is in reality an end organ" disease rather than a true parathyroid disease Secondary hyperparathyroidism is thought to play a part in the pathological physiology of osteomalacia—a condition in which the parathyroid glands are found to be hyperplastic This is further discussed in the chapter on Osteomalacia In renal glomerular insufficiency with elevation of the serum inorganic phosphate* and depression of the serum calcium parathyroid hyperplasia is almost constantly seen Some investigators attribute the osteitis fibrosa of this condition to secondary hyperparathyroidism others to the renal failure *per se* (See Osteitis Fibrosa Cystica Generalisata) Space does not permit a discussion of the theoretical issues involved However there is general agreement as to the pertinent practical consideration Removal of parathyroid tissue is *not* of benefit in renal osteitis but rather the reverse

This section is devoted to primary hyperparathyroidism hypoparathyroidism pseudohypoparathyroidism and tetany

PRIMARY HYPERPARATHYROIDISM

Definition Primary hyperparathyroidism is a condition in which chemical abnormalities of the serum and extracellular fluid result from overproduction of parathyroid hormone Osteitis fibrosa cystica generalisata may or may not be present

Etiology The immediate causes of primary hyperparathyroidism are single or multiple adenomas of the parathyroid glands primary hypertrophy and hyperplasia of all parathyroid tissue and carcinoma As the name implies the primary hypertrophy and hyperplasia is an entity distinct from the secondary hyperplasia seen with osteomalacia and renal failure If it involves a "tropic stimulus the source or nature of such stimulus is entirely obscure Available evidence is strongly against the existence of pituitary parathyrotropic hormones The cause of adenoma formation is also obscure The relatively common association of pancreatic islet cell tumors and pituitary tumors with those of the parathyroid suggests a common etiological factor but throws no light on what it may be

Incidence Primary hyperparathyroidism is a relatively rare disease After the chemical and clinical criteria for diagnosis had been established and cases were being actively sought for at the Mayo Clinic and the Massachusetts General Hospital it required twenty years for each clinic to accumulate 100 cases Adenomas were found in approximately 90 per cent of these and primary hyperplasia and hypertrophy in 10 Carcinoma is extremely rare Adenomas appear about twice as frequently in women as in men

Morbid Anatomy Adenomas vary greatly in size ranging from minute tumors barely visible macroscopically to large growths displacing the esophagus easily palpable *in vivo* and resembling thyroid nodules With primary hyperplasia and hypertrophy the weight of the combined glands has ranged from 2 to 70 gm with the upper glands quite consistently larger than the lower

Microscopically the functioning adenomas are composed of chief cells water clear (wasserhelle) cells admixtures of the two and less commonly of pale oxyphil cells Among the chief cells considerable variability in nuclear size with giant nuclei and multinucleated cells are not infrequent and are not criteria of malignancy With primary hyperplasia all the parathyroid cells are much larger than wasserhelle cells and are also clear

When the bones are affected they show osteitis fibrosa cystica generalisata as discussed in the section on Diseases of Bones

When the kidneys are affected they may develop nephrolithiasis or nephrocalcinosis both frequently complicated by pyelonephritis

Pathological Physiology and Chemistry As a result of overproduction of parathyroid hormone by the adenomatous or hypertrophied glands there ensues (1) a decrease

* Hereafter the serum inorganic phosphate will be here termed the serum phosphorus for the sake of brevity

in renal tubular phosphorus reabsorption and (2) a decrease in serum phosphorus This results in a relative undersaturation of the extracellular fluids with respect to calcium phosphate with the result that (3) there is a rise in serum calcium If the calcium intake is adequate and the additional calcium available in the gastrointestinal tract the bones may not be affected If it is inadequate osteitis fibrosa generalisata frequently develops As a result of the rise of serum calcium (4) the urine calcium rises An effect of the parathyroids directly on bone independent of the renal effect has been established This suggests that the osteitis fibrosa may be a direct effect of parathyroid hormone The majority of cases of hyperparathyroidism now being recognized *however have normal bones*

The cardinal biochemical signs of primary hyperparathyroidism are a lowered serum phosphorus an elevated serum calcium and an elevated urine calcium (A low calcium diet is generally employed for at least three days to evaluate urinary calcium excretion A low *phosphorus* diet frequently exaggerates all three signs in borderline cases) When the bones are affected there is in addition an elevated serum alkaline phosphatase (The urine phosphorus is not of diagnostic value after a steady state of disease has been reached)

The signs of primary hyperparathyroidism become more difficult to interpret with the appearance of renal failure a very common sequela if treatment is not instituted Renal failure results in (1) a rise in serum phosphorus (2) a relative supersaturation of the extracellular fluid with respect to *calcium phosphate (3) a fall of serum* calcium and (4) a fall of urine calcium It is apparent that a point will be reached when the diagnosis can no longer be made At this point however removal of the tumor does little to improve the patient

A further difficulty in the diagnosis of primary hyperparathyroidism arises from the finding that some patients have hypophosphatemia without accompanying hypercalcemia (Bogdonoff *et al*) It has been suggested that the parathyroid glands may elaborate two distinct hormones one specifically inhibiting renal tubular reabsorption of phosphate the other directly mobilizing bone substance

Symptoms Symptoms in primary hyperparathyroidism may result from the hypercalcemia the hypercalciuria and the bone disease when it is present Hypercalcemia results in anorexia weakness fatigability difficulty in swallowing nausea vomiting constipation and hypotonicity of the muscles and ligaments the last at times resulting in striking double jointedness These are presumably a reflection of the known effects of hypercalcemia in depressing the sensitivity to electrical stimuli of ganglia and peripheral nerves The latter can be demonstrated directly by the use of Erbs test Shortening of the Q T interval in the electrocardiogram is found in some cases Two lesions in the eyes result from hypercalcemia— band keratopathy in which bands of opaque material are found beneath Bowman s capsule in lines parallel to and within the limbus especially in the palpebral fissure and conjunctival crystals located medially and laterally to the limbus also in the palpebral fissure Both lesions *often require a slit lamp for recognition*

Hypercalciuria may result in nephrolithiasis and the appearance of calcium oxalate or calcium phosphate stones is often the presenting symptom of the disorder In other cases nephrocalcinosis may result with progressive renal damage Infection of the urinary tract is common with both complications

The bone disease when it occurs is osteitis fibrosa cystica generalisata It is dealt with in the section on Diseases of Bones Of special value in diagnosis are the loss of lamina dura about the teeth the finding of subcortical bone resorption and the presence of "cysts and "brown tumors especially the epulis of the jaw

Differential Diagnosis Hypercalcemia is found with vitamin D overdosage with certain bone diseases and associated with renal damage with prolonged excessive in*take of calcium and alkali* In all of these the history is of paramount importance in all of them the serum phosphorus is characteristically normal (although it may rarely be depressed with hypervitaminosis D) In osteoporosis the serum alkaline phosphatase is normal and in Paget s disease the x ray picture is usually diagnostic Hypercalcemia and hypercalciuria are also often found in multiple myeloma and in sarcoidosis In these diseases the serum phosphorus is characteristically normal and the serum globulin frequently elevated The serum alkaline phosphatase is almost always normal in spite of bone disease in myeloma and is generally normal in sarcoidosis Metastatic malignancy in bone may produce hypercalcemia and resemble hyperparathyroidism closely as the serum phosphorus *although generally normal* may be depressed In this as in all the above disorders a *normal lamina dura about the*

teeth helps to exclude hyperparathyroidism as the cause of the bone disease

Hypercalciuria is characteristic of all hypercalcemic states except that due to prolonged excessive intake of calcium and alkali Hypercalciuria without hypercalcemia occurs in idiopathic hypercalciuria" a renal disease often accompanied by coccal infection and in "renal tubular acidosis In neither is the serum calcium elevated in the latter metabolic acidosis is present When metabolic bone disease occurs in these conditions it is osteomalacia the reader is referred to the article on the subject

The differential diagnosis of osteitis fibrosa cystica is discussed in the appropriate place

Prognosis Primary hyperparathyroidism responds very satisfactorily to surgery The frequency with which a second adenoma occurs in patients from whom one has been removed is greater than that with which primary hyperparathyroidism occurs in the population at large When primary hyperplasia and hypertrophy has been present (and partial resection done) persistence of hypercalciuria and recurrence of hypercalcemia are common

Treatment The treatment of primary hyperparathyroidism is surgical Search for adenomas may involve dissection of the mediastinum as well as the neck Adenomas should be removed *in toto* With primary hyperplasia and hypertrophy (the presence of which should be confirmed by frozen section) small (*ca* 250 mg) sections of two glands with blood supply should be left and the rest removed Postoperatively severe tetany may be expected where there has been bone disease It may require vigorous therapy with calcium by vein (*e g* 30 ml of 10 per cent calcium lactate in 1000 ml of normal saline) and by mouth (*e g* 6 teaspoons calcium lactate a day) and with vitamin D by mouth (*e g* 50 000 units a day) until the bone disease is healed Therapy must then be promptly stopped before it results in hypercalcemia

HYPOPARATHYROIDISM

Definition Hypoparathyroidism is a condition in which chemical abnormalities of the serum and extracellular fluid result from underproduction of parathyroid hormone

Etiology The commonest cause of hypoparathyroidism is the inadvertent removal of or damage to parathyroid tissue during thyroid surgery The resulting disease may be temporary if enough tissue was left or if edema and hemorrhage were precipitating factors Rarely hypoparathyroidism appears without apparent cause Some cases are preceded by acute systemic infections others are accompanied by mild infection of mouth skin and nails with monilia (It is not clear whether the monilia is a cause or a result of the disease) In the latter group familial incidence has been reported The disease tends to develop in children under fifteen or in adults over forty and is rare between these ages for reasons not apparent The frequency of its coexistence with Addison s disease is significantly above the probability of chance

Incidence "Idiopathic" hypoparathyroidism is a rare disease only 34 cases had been reported by 1946 The incidence of postoperative hypoparathyroidism in various clinics naturally varies

Morbid Anatomy In "idiopathic" hypoparathyroidism the parathyroid glands have been reported to show complete or almost complete replacement of parenchymal tissue by fat The finer blood vessels of the brain especially those of the basal ganglia may be surrounded by hyalin deposits which calcify The bones may be abnormally dense

Pathological Physiology and Chemistry As a result of a decrease in parathyroid hormone secretion there ensues (1) an increase in renal tubular phosphorus reabsorption (2) a rise in serum phosphorus and (3) a fall in serum calcium As a result of the fall in serum calcium (4) the urine calcium falls reaching essentially zero at serum levels below 7 mg per 100 ml

The cardinal biochemical signs of hypoparathyroidism are thus an elevated serum phosphorus a lowered serum calcium and a lowered urine calcium (The urine calcium is occasionally normal or even elevated in hypoparathyroidism—a phenomenon often associated with coccal pyelonephritis or prolonged calcium chloride medication) The lowered serum calcium results in increased excitability of peripheral nerves and ganglia and hence in tetany and symptoms referable to hyperactivity of the autonomic system

Symptoms Most of the symptoms in hypoparathyroidism can be explained as results of the hypocalcemia a few are unexplained The most prominent manifestation of hypocalcemia is *tetany* The first sign of this is often a sensation of numbness and tingling in the fingers and toes

or about the lips Laryngeal stridor with prolonged crowing inspiration dyspnea and cyanosis are not infrequently seen occasionally leading to a mistaken diagnosis of vocal cord paralysis As the tetany becomes more severe cramps of individual muscles and finally tonic contractions of muscle groups appear In the hand and arm this results in the characteristic "accoucheur s position Gastric pain nausea and vomiting may accompany severe tetany Generalized convulsions have frequently been described with severe hypoparathyroidism In some cases there are an aura tongue biting urinary and fecal incontinence and post seizure coma and electroencephalograms support the impression that hypocalcemia is acting to trigger a pre-existing grand mal Others in which both the seizure pattern and the electroencephalograms are atypical presumably represent a direct effect of hypocalcemia on the central nervous system In all great improvement occurs when the hypocalcemia is eliminated The differential diagnosis of tetany is dealt with below

Papilledema *and increased intracranial* pressure are relatively frequent accompaniments of hypoparathyroidism They disappear with therapy Calcifications about the smaller vessels of the brain especially *those of the basal ganglia often visible in* skull x rays are commonly seen in hypoparathyroidism These do not regress with therapy Neither of these lesions is found with hypocalcemia of other cause Cortical cataracts are common in hypoparathyroidism and in other disorders involving hypocalcemia The underlying mechanism for all these lesions is obscure

Defects in ectodermal structures that may be found in hypoparathyroidism involve the teeth nails skin or hair When hypoparathyroidism develops before the permanent teeth are mature they may show shortening and malformation of the enamel organ and shortening of the roots The nails which may be malformed and brittle are sometimes infected with moniliasis as already mentioned The skin is sometimes coarse and dry the head hair patchy and thin the eyebrow axillary or pubic hair may be scant or absent

Diagnosis A number of clinical tests may be employed to reveal the presence of latent tetany Chvostek s sign is sought by tapping the finger over the facial nerve A positive response consists of twitching of the muscles of the mouth and with severer cases of the nose and eyelids A positive Chvostek s sign is usually but not invariably present in tetany A positive response occurs commonly in normal persons Trousseau s sign is sought by producing ischemia to peripheral nerves by inflating a pressure cuff on the arm above systolic pressure for 3 minutes A positive response is frequently elicited in patients with latent *tetany Erb s sign is sought by* applying a galvanic current to the skin over a peripheral motor nerve and measuring the minimal current necessary to produce a muscle contraction upon cathode opening With latent tetany a response appears with 5 milliamperes or less

The characteristic serum values have been discussed The electrocardiogram may show a prolonged Q T interval with hypocalcemia

The combination of increased intracranial pressure papilledema and a history of convulsions in hypoparathyroidism has often led to a mistaken diagnosis of brain tumor The relationship of epilepsy to tetany has been discussed

Prognosis In the hypoparathyroidism which follows thyroid surgery recovery *often occurs even after weeks or months* Therapy should be carefully withdrawn at intervals in such cases until it is clear that no recovery will ensue Idiopathic hypoparathyroidism requires continuous therapy *and if this is adequate new cataracts* should not develop The prognosis of classic or atypical epilepsy in hypoparathyroidism is excellent if adequate therapy can be maintained

Treatment Acute hypocalcemic tetany requires prompt treatment with calcium intravenously (*e g* calcium lactate 10 per cent solution 10 to 30 ml intravenously in 1000 ml normal saline) given as often as necessary to control symptoms Simultaneously calcium (*e g* calcium lactate 4 gm 6 times daily) and vitamin D (*e g* 50 000 units daily) should be started by mouth The dosages should be reduced when the serum and urine calcium are brought to normal and maintained in quantities found adequate to keep them so The Sulkowitch test for urine calcium which the patient can perform provides a useful index of the adequacy of therapy AT 10 (Hytakerol) may be used (*e g* 0 5 to 1 ml orally each day) in place of vitamin D for maintenance therapy It has the advantage of more rapid action the disadvantage of greater cost

TETANY

The symptom complex of tetany and the diagnostic tests for latent tetany have been

Schema for the Classification and Differential Diagnosis of Tetany

CAUSE	SERUM				URINE	
Hypocalcemia	*Ca*	*P*	*pH*	*CO_2*	*Ca*	*pH*
Low Ca intake	low	low	normal	normal	low	indeterminate
High intestinal Ca loss						
1 Vitamin D lack	low	low	normal	normal	low	indeterminate
2. Sprue	*low*	*low*	*normal*	*normal*	*low*	*indeterminate*
3 Diarrhea	low	low	normal	normal	low	indeterminate
High urinary Ca loss						
1 Essential hypercalciuria	low	low	normal	normal	high	indeterminate
2. Renal tubular acidosis	low	low	low[1]	low	high	high
Elevated serum P						
1 Hypoparathyroidism	low	high	normal	normal	low	indeterminate
2 Glomerular insufficiency	low	high	low[1] or normal	low or normal	normal	indeterminate
3 Excessive ingestion	low	high	normal	normal	low	indeterminate
Alkalosis						
Respiratory	normal	normal	high	low or normal	normal	high
Metabolic						
1 Excessive alkali intake	normal	normal	high	high	normal	high
2 Persistent vomiting	normal	normal	high	high	normal	high
3 Excessive H loss to cells and urine	normal	normal	high	high	normal	low → high[2]

Ca = Calcium *P = Inorganic phosphate* *CO_2 = Carbon dioxide content*

[1] Note that in renal tubular acidosis and in renal insufficiency the serum acidosis tends to oppose the effect of hypocalcemia

Excessive H loss with high *p*H may occur when urinary NH_4 is high

discussed under hypoparathyroidism The present section is devoted to its etiology and differential diagnosis

Tetany may be precipitated by hypocalcemia or alkalosis or both Whereas low magnesium tetany has been described its extreme rarity renders it negligible from the clinical point of view Tetany has frequently been observed with potassium deficiency even without the commonly associated alkalosis As intracellular *acidosis* is characteristic of potassium deficiency *this* suggests that the difference between extra and intracellular *p*H may be important in the etiology of tetany In the accompanying table are summarized the causes of tetany with the essential laboratory data

The *causes of hypocalcemia* may be divided into those in which the calcium intake is inadequate those in which gastrointestinal calcium loss is excessive those in which urinary calcium loss is excessive and those in which the serum phosphorus is elevated (and the serum calcium depressed)

Inadequate intake of calcium as a cause of hypocalcemia probably does not occur in the United States Excessive calcium loss via the gastrointestinal tract occurs in hypovitaminosis D in "resistance to vitamin D" in the sprue syndrome in which vitamin D and calcium soaps are lost because of steatorrhea and in severe diarrhea in which calcium-containing secretions are lost In all these conditions the tetany should respond to measures designed to increase calcium absorption *e g* vitamin D calcium salts control of diarrhea Excessive calcium loss via the kidneys occurs in "essential hypercalciuria" and in "renal tubular acidosis" but tetany is rare in these conditions

Elevated serum phosphorus and lowered serum calcium are found in hypoparathyroidism and in glomerular insufficiency in the former calcium is usually absent from the urine in the latter urinary calcium is often decreased but seldom absent The two conditions are generally easily distinguished by the presence or absence of other signs of renal failure *e g* nitrogen retention *The intravenous injection of 200 units* of parathyroid extract should clarify the differential diagnosis if any doubt remains This results in marked phosphaturia in hypoparathyroidism (but see the section on Pseudohypoparathyroidism) and in virtually none in renal failure In infants fed cow s milk hyperphosphatemia with hypocalcemia and tetany has been reported in the absence of renal failure Here the amount of phosphorus fed exceeds the amount filtered by the glomeruli at normal

serum levels In glomerular insufficiency the tetany should respond to measures designed to lower the serum phosphorus *e g* oral aluminum hydroxide and raise the serum calcium *e g* vitamin D Alkali therapy for correction of acidosis may have to be withheld The therapy of hypoparathyroidism has been discussed

The *causes of alkalosis* may be divided into those in which respiratory loss of carbon dioxide is excessive those in which alkali intake is excessive and those in which loss of extracellular hydrogen ions is excessive In the last category are included excessive loss of gastric acid and excessive loss of hydrogen ions from the extracellular fluid to the intracellular fluid and to the urine

Hyperventilation is not infrequently a manifestation of psychoneurosis With a sudden increase in respiratory rate serum carbonic acid is lowered by loss of carbon dioxide in the lungs the serum *p*H is elevated and tetany may follow The condition is readily remedied by having the patient breathe into a paper bag or inducing him to decrease his respiratory rate In this form of alkalosis alone serum bicarbonate is normal or low

Excessive intake of alkali and excessive loss of gastric acid may produce alkalosis and tetany The diagnosis which should be clear if a history is obtainable is supported by the finding of an elevated serum bicarbonate and an alkaline urine The tetany should respond to measures designed to prevent vomiting and of course to cessation of alkali therapy Excessive secretion of adrenal cortical hormones (as in primary aldosteronism) or treatment with analogous steroids may lead to loss of extracellular fluid hydrogen ions both to the urine and to the cells A concomitant depletion of potassium which is essential for the loss to cells aggravates the urinary loss as well The tetany which results responds to the alleviation of the hormonal excess and the repletion of body potassium

PSEUDOHYPOPARATHYROIDISM

Definition Pseudohypoparathyroidism is a condition in which the chemical abnormalities of hypoparathyroidism exist in the presence of normal or hyperplastic parathyroid glands and in the absence of renal glomerular insufficiency It is generally part of a syndrome involving developmental changes of bone An essential feature in its recognition is the demonstration of nonresponsiveness to parathyroid extract

Etiology Nothing is known of the etiology of pseudohypoparathyroidism Resistance to parathyroid extract is found but circulating antibodies or precipitins have not been demonstrated Certain elements of the disorder suggest a relationship to the hereditary disorders achondroplasia and myositis ossificans progressiva Since the characteristic epiphysial changes and metaplastic bone growth are found in these conditions in the absence of serum chemical abnormalities it appears that the anatomical and hormonal features are related genetically but are not interdependent

Incidence Pseudohypoparathyroidism is a very rare disease the incidence of which cannot be accurately evaluated Since it was first described in 1942 a few new cases have been reported and a few cases formerly classified as idiopathic hypoparathyroidism have been reclassified under this heading

Morbid Anatomy The essential features of morbid anatomy are the presence of normal or hyperplastic parathyroid glands the short stature and round face found in most patients the shortened metacarpals and metatarsals and ossifications in skin and tendon

Pathological Physiology and Chemistry The sequence of chemical events in this condition is the same as that in idiopathic or postoperative hypoparathyroidism and the cardinal biochemical signs are the same with the significant difference that parathyroid extract given intravenously in a dose which produces marked hyperphosphaturia in the former conditions produces little or no change in urine phosphate in this one As might be anticipated it fails also to lower the serum phosphorus or to raise the serum calcium

Symptoms The symptoms and signs of pseudohypoparathyroidism include all those of idiopathic hypoparathyroidism with the possible exceptions of papilledema and associated moniliasis In addition patients characteristically show short stature and roundness of the face

In most cases certain of the metacarpal and metatarsal bones are abnormally shortened as a result of early epiphysial union The corresponding shortness of fingers and toes is readily apparent In many there are found metaplastic islands of true bone in skin and connective tissues these features have suggested a relationship with achondroplasia and myositis ossificans progressiva In Browne s case a mother and daughter both had stigmata of achondro-

plasia as well as multiple exostoses and the daughter had in addition pseudohypoparathyroidism Mental deficiency is present in most cases and does not depend upon a history of convulsions

Diagnosis This is established by finding the serum chemical abnormalities of hypoparathyroidism without those of glomerular insufficiency and by demonstrating less than a twofold increase in urinary phosphorus excretion following administration of 200 units of active parathyroid extract intravenously (The activity of the extract should be checked simultaneously in a normal subject) The features discussed above may obviously be of considerable help in diagnosis The demonstration of parathyroid tissue by biopsy establishes the diagnosis unequivocally

Treatment The treatment is that of hypoparathyroidism in general larger doses of AT 10 may be required than are needed in idiopathic hypoparathyroidism

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DISEASES OF THE PITUITARY GLAND

The Hormones of the Anterior Lobe

The hormones of the anterior lobe are proteins or polypeptides Of these six are now considered to be chemical and biological entities They have been purified to varying degrees and repair specific anterior lobe defects *in hypophysectomized* animals These six are the growth hormone or somatotrophin prolactin or the lactogenic hormone the follicle stimulating hormone the luteinizing or interstitial cell stimulating hormone thyrotrophin and adrenocorticotrophin or corticotrophin

The materials now available however homogenous however pure however well characterized should be considered representatives of these hormones rather than the actual secretions themselves Detection of biological activity in the blood stream and in the urine is often difficult and satisfactory assay is only now being approximated in a few instances Precise comparisons between the properties of extracted agents and those predicted or inferred from *physiological study and from the study of* disease in animals and man are still required Extracted material may well represent associations between a true hormone and the proteins of the cells that make it and may represent this association in various steps of the manufacture of this hormone On occasion even artifacts may appear Nevertheless the current accomplishments fathered by advances in protein chemistry are great indeed and several *available agents may approximate closely* the secretions as delivered to the blood stream

The Growth Hormone or Somatotrophin The existence of this hormone was inferred from the excesses and deficiencies of somatic growth in man as exemplified by gigantism and acromegaly on the one hand and by dwarfism on the other Subsequently dwarfism was produced by hypophysectomy in dogs (Aschner 1910) and in frogs and rats (*Smith* 1916–1926) The hormone is defined by its capacity to repair this defect in general body growth following hypophysectomy and to carry this growth to characteristic excess when given in large amounts

Since the first effective pituitary extracts of Evans and Long (1921) great progress has been made in describing the composition of active material but much of this progress is recent and a matter still for vigorous discussion A relatively homogene*ous protein by electrophoretic diffusion* and solubility tests was extracted from beef pituitaries by Li Evans and Simpson (1944–1945) and a crystalline preparation was obtained in greater abundance from the same source by Wilhelmi Fishman and Russell (1948) Active agents of *high purity have now been obtained from* fish sheep horse pig monkey and human pituitaries Li (1957) has reported molecular weights of 46 000 for the bovine agent 25 400 for that of the monkey and 27 100 for that of man He considers the first of these to be a branched polypeptide chain of 396 amino acid residues and those of monkey and of man to be single polypeptide chains with 25 400 and 27 100 residues respectively Postulates as to certain *details of structure have been made* Products obtained by other methods may well differ and those from other species would be expected to Some nuclear structure common to these diverse molecules may account for the correspondence among them in physiological effect

Important species differences in the growth response to principles from a given animal source are now appreciated and may well be critical for work in man The *hypophysectomized rat which has for* years provided the governing assay is sensitive to active products from all mammalian species thus far studied Preparations from fish pituitaries (hake pollack) however exert no effect The hypophysectomized monkey will not respond to the bovine or pig growth hormones but monkey pituitary extracts induce nitrogen retention (Knobil Wolf Greep and Wilhelmi 1957) and repair of the atrophied costal cartilage has been described Nitrogen retention in patients with pituitary defects has now been induced by monkey and human proteins prepared by Rabin and by Li (1957

Beck *et al* Henneman *et al* Bergenstal) Forthcoming details should provide a better account of the properties of growth hormone in man than the hitherto irregular and often uncertain results given by the use of bovine material

The influences of somatotrophin upon the organism are relatively well generalized and are expressed by growth and the immediate metabolic concomitants and consequences of the growth process and by a number of other chemical events not so surely related to growth The defects in the thyroid adrenal cortex and gonads that follow hypophysectomy are repaired incompletely or not at all these structures requiring specific trophic hormones for full restitution of function All influences of the growth hormone on these target organs however are not excluded and come up for consideration from time to time Except for these tissues the effects of somatotrophin on the animal dwarfed by hypophysectomy are fairly uniform Skin musculature viscera and the cardiovascular system respond together Even when gigantic overgrowth is induced as in the hypophysectomized or normal rat this harmony largely prevails although excrescences of cartilage bone and the fibrous elements of the skin mark points of special sensitivity to the growth hormone Neoplasia may be induced in normal rats lymphosarcomas arising especially about the tracheobronchial tree and tumors of the adrenal medulla are conspicuous (Moon *et al* 1950) There is little or no established influence of the growth hormone on the brain

There are complex interrelations between the effects of somatotrophin and those of other agents on several growth processes Insulin with its own anabolic influence is a necessary co factor for the general growth response thyroid secretion is necessary for optimal response 11 Oxygenated steroids from the adrenal cortex oppose somatotrophin when present in excess The growth hormone is essential for proliferation of the mammary tree serving in synergism with prolactin and with adrenal and gonadal steroids

Somatotrophin or some companion still not disassociated by the chemists exerts profound influences upon carbohydrate metabolism which have been much studied but which are still imperfectly understood Several of these influences are exerted by preparations comprised chiefly or entirely of the growth hormone The physiological mechanisms involved are complex and often a subject of disagreement The reviews of Bennet and Evans in Pincus and Thimann and Young will serve to introduce the reader to details Roughly put the animal lacking a hypophysis is exquisitely sensitive to insulin cannot maintain its glycogen stores during fasting and does not show the usual evolution of diabetes mellitus after pancreatectomy (Houssay phenomenon) Extracts restore the state prior to hypophysectomy and may furthermore induce an insulin resistant diabetes in the normal animals of some species (dogs for example) followed by islet cell degeneration and a permanent insulin sensitive diabetes enduring after cessation of treatment (Young s or metahypophysial diabetes) The growth hormone apparently serves to maintain one element of the fasting carbohydrate stores (muscle glycogen glycostatic effect) It is or else closely associated with the diabetogenic agent effective in the normal dog in which it appears to act independent of the adrenal cortex Thus it seems likely that the association of unusual growth and diabetes mellitus in acromegaly may well be due to excesses of a single agent the capacity of the individual pancreas to secrete insulin determining whether diabetes will or will not occur

The adrenal hormone secreted in response to ACTH is likewise diabetogenic in certain species (man and partially depancreatized or force fed rat) and antagonizes the action of insulin These are presumably the experimental analogues of the diabetes mellitus of Cushing s syndrome The precise nature of the interrelationships between the activities of the growth hormone and those of the adrenal steroids on carbohydrate metabolism is obscure and it is not clear whether the liability of patients with hypopituitarism to spontaneous hypoglycemia or their sensitivity to insulin is due chiefly to the lack of the one or of the other or of both

The amounts of the growth hormone circulating in the human system can be assessed now only by its effects No workable biological assay of the agent in body fluids is available although its presence has been detected in the plasma of acromegalics At the moment therefore estimates depend on a congeries of clinical and intrinsically nonspecific laboratory techniques Though a good deal can be accomplished by sophisticated use of what we have better methods are badly needed

Prolactin (Lactogenic Hormone, Luteotrophin) This agent induces lactation in the suitably prepared breast and is apparently

necessary for the growth and development of the mammary apparatus Highly purified proteins obtained by A White and by Li *et al* from beef and sheep pituitaries (1942) were much alike Li has subsequently reported a molecular weight of 33 000 for sheep prolactin with an assignment of amino acid composition It contains no carbohydrate In the hypophysectomized rat complete replication of the architecture of the breast in pregnancy together with lactation depends upon the properly balanced action of prolactin somatotrophin estrogen progesterone and adrenocorticotrophin (Lyons 1943 1955) Such complex synergisms may be expected wherever prolactin is concerned Lactation first demonstrated with crude effects in rabbits (Stricker and Grueter 1928) has now been induced in women and men by Huggins and Dao (1954) Influence on breast growth in the human is hard to evaluate Regression of some breast tumors after hypophysectomy may be due to withdrawal of prolactin support Purified prolactin evokes secretion of progesterone from the corpus luteum of the rat by the action of the luteinizing hormone on the prepared ovary (Astwood) So far this function leading to the use of the name "luteotrophin has not been identified in other species but may exist there Assay is now usually determined by the response of the crop gland of the pigeon (Riddle and Bates 1932 1933) Active material so measured is present in human urine and according to Segaloff shows increments during the menstrual cycle suggesting participation in the control of the human ovary Even broader functions may exist as certain *somatotrophic* influences on liver and cartilage have been shown in other *species*

The Follicle Stimulating Hormone (FSH) The best products from the chemical stand point indicate a glycoprotein stimulating and necessary for the growth of the ovarian follicle but requiring a co factor provided by the luteinizing hormone (LH) at least for estrogen secretion and for ovulation In the male spermatogenesis is facilitated although androgens alone arising in response to LH may suffice to support spermatogenesis in some species In all probality there is some systematic scheme whereby FSH and androgens cooperate in the control of the seminiferous epithelium with experimental conditions and species variations dramatizing first one aspect and then the other but leaving the over all pattern incoherent and inconsistent to us for the moment

Normal human urine contains a gonadotrophin or gonadotrophins which may be increased to as much as tenfold or more by removal of the gonads or by the normal involution of the ovaries at the menopause Unfortunately this material has not been sufficiently purified to permit precise chemical definition It has follicular growth provoking properties and excites estrogen secretion and if the analogy with anterior lobe extracts holds may be dual in composition Unlike chorionic gonadotrophin abundantly secreted by the human placenta during pregnancy it requires no pituitary co factor for its influence on the ovaries acting in hypophysectomized animals Spermatogenesis and androgen production are facilitated by suitable doses in the male The material may be assayed with fair efficiency either by its effects on the ovaries or by its indirect effects on the uteri of immature rats or mice More recently the response of the ventral prostate of the rat has served to define the interstitial cell stimulating properties The results are of great value in determining whether the pituitary body or the gonads are primarily responsible for gonadal deficiency High values bespeak primary gonadal defect low values indicate pituitary defect if repeatedly obtained Normal values are ambiguous The administration of estrogens (or androgens in sufficient doses) inhibits the secretion of these materials by the anterior lobe

The administration of foreign gonadotrophins to man for purposes of exciting the ovarian follicles to grow and to secrete estrogens has been disappointing The difficulties may lie in the products in antihormone *formation in imperfect knowledge of the* character of the defect in the subject and *in failures to imitate nature s* delicate synergism between FSH and LH There is every reason to believe that all factors are involved

The Luteinizing Hormone (LH) or Interstitial Cell Stimulating Hormone (ICSH) This is a glycoprotein Purified (or pure) agents from swine (Chow *et al* 1942) and sheep (Li *et al* 1940–42) differ chemically This hormone is a synergist and a companion hormone to FSH It may co operate with FSH in maturing the ovarian follicle and is essential to ovulation and formation of the corpus luteum It is now usually held responsible in great part for *estrogen secretion In rats at least* continued secretory activity of the formed corpus luteum is attributed to luteotrophin rather than to LH The trophic influence of LH on the interstitial cells of the ovaries of rats

although used for assay has not yet acquired real physiological meaning Luteinizing hormone is however a powerful stimulant of androgen production by the interstitial cells of the testes in all species studied The gonadotrophic material in the urine of normal and castrate humans has LH like propensities despite the common practice of designating only the FSH like properties Assays are discussed under FSH Luteinizing hormone of animal pituitary origin has not been successfully given to man although the somewhat similar human chorionic gonadotrophin is quite potent

The Thyrotrophic Hormone (TSH) This agent is defined by its capacity to repair the atrophy and secretory defects of the thyroid gland that follow hypophysectomy Sufficient doses induce hypertrophy and hyperplasia of the cellular elements of the thyroid and the secretory excess of hyperthyroidism Discharge of thyroxin from the follicles is accelerated a proteolytic enzyme serving to release the hormone from the intrafollicular protein thyroglobulin The manufacture of new hormone to replace that lost is accelerated Extraction of iodide from the blood stream is sharply increased

Thyrotrophin itself has not thus far been isolated or sufficiently characterized A molecular weight of 10 000 has been estimated although it may well be less (Ciereszko 1945 Hays and Steelman 1955) It appears to be a glycoprotein Pituitary extracts chiefly thyrotrophin exert effects in the absence of the thyroid Exophthalmos is a notable example its evolution depends in part upon the deposition of hydrophilic mucopolysaccharides in the ground substance of the connective tissue of the orbit The striated musculature including that of the orbit may suffer such infiltrates Movement of fat from body depots into the liver and elsewhere including the striated musculature has been noted How many of these influences are due to thyrotrophin and how many to associated agents is uncertain Dobyns and Steelman (1953) suggest an exophthalmos inducing factor" separate from thyrotrophin measuring exophthalmos by the response in the fish Fundulus

Assays for thyrotrophin in human body fluids have permitted detection of activity in both blood and urine but have not advanced to the point of simplicity and reliability Among the most interesting techniques is that of D Angelo (1951) Use of the tadpole in which metamorphosis is suspended by starvation permits detection of both thyrotrophin and thyroid hormone in the same serum Advancement of metamorphosis occurs with either agent but the preponderance of thyrotrophin is indicated by hypertrophy of the thyroid epithelium Thus determined thyrotrophin has been detected in normal serum The thyrotrophic theory of Graves disease has not been supported by the finding of excess thyrotrophin in the serum In progressive exophthalmos high values have been found but agreement on the point has hardly been reached In acromegaly elevated values may appear but not consistently related to the occurrence of hyperthyroidism

Thyrotrophin largely of beef origin will provoke hyperthyroidism in man Increments in protein bound iodine (including the butanol extractable moiety chiefly thyroxin) and increased uptakes of iodine measured by radioactive iodine are induced The process could not be sustained for long periods by the older extracts antibodies rising in the host to terminate the influence of the foreign hormone More recently thyrotrophin has been injected to assess the the reactivity of the thyroid in hypothyroidism A response indicated that the thyroid itself is not at fault and suggests hypopituitarism Standardization of this procedure has hardly been achieved and the wisdom of general use of our still impure products is questionable to this writer (For details of proposed methods see Williams text 1955)

Adrenocorticotrophin (ACTH, Corticotrophin, corticotropin) * This hormone exerts a trophic influence upon the adrenal cortex repairing its morphological and secretory deficiencies in the hypophysectomized animal and inducing hyperplasia and hypersecretion in the normal animal The original proteins isolated by Sayers Li and their colleagues (1943) were estimated to have molecular weights approaching 20 000 but following the work of Astwood and his associates (1951–1952) it became apparent that degradation to much smaller polypeptide moieties results in no loss of biological activity Shepherd and Bell have obtained a virtually homogeneous polypeptide from hog pituitary (β-corticotrophin) which has a sequence of 39 amino acids nearly identical to the sequence in α-corticotrophin isolated from sheep pituitary by Li and his group (1955) The estimated molecular weight is 4000 to 5000 By means of pepsin as many as 11 to 15 amino acid residues may be split off from the C terminal (not from the N terminal) end with preservation of activity so that the essential

* Revised by Dr Nicholas P Christy

hormone may be a still simpler substance

A controversy exists as to the biological nature of adrenocorticotrophin i e whether it is one substance or several For example the older ACTH protein enhanced adrenal weight to a greater degree than it did steroidgenesis whereas the newer ACTH peptide produced reverse effects Furthermore Reinhardt Geschwind and Li (1951) and Young and Stack Dunne (1951) have isolated pituitary fractions with different ratios of adrenal weight augmenting to steroidogenic potency and have suggested the possibility that there are two corticotrophins with these separate activities It is difficult to state with certainty at this time whether the adrenal weight augmenting material is a corticotrophin or whether it is related more closely to somatotrophin (Young) Its relation to the purified polypeptides described above is unknown A third substance melanocyte stimulating hormone or MSH (analogous to the melanophore-expanding principle found in the intermediate lobe of the amphibian pituitary) has aroused interest as a result of earlier difficulties in separating pigmentary and adrenocorticotrophic effects of various pituitary fractions administered to man (Lerner 1955) and also in view of the demonstration by Sulman (1956) and others of elevated blood concentrations of MSH in clinical situations characterized by demonstrably high plasma concentrations of ACTH (*e g* Addison s *disease) It now seems likely that MSH is* truly a distinct substance Thing and Li have achieved electrophoretic separation of MSH from ACTH and Li and Harris and Roos have isolated a substance with a sequence of 18 amino acids and a minimum molecular weight of about 2000 Corticotrophin and MSH have a short amino acid sequence in common which may explain in part why there is feeble but definite MSH activity in pure ACTH

The cellular origin of ACTH or of the ACTH complex in the pituitary gland is not definitely known Much circumstantial evidence favors the basophil For example Kilby Bennett and Sprague (1957) found hyaline and other changes exclusively in basophils of patients treated with corticotrophin (or cortisone) and Marshall (1951) provided immunological evidence that ACTH antihormones (antisera) localized only in basophilic cells

The mechanisms regulating ACTH release from the pituitary are complex and controversial At least two seem well established Corticotrophin release rate is inversely related to the level of circulating adrenal cortical glucocorticoid (Sayers 1950) Adrenal cortical extract brings about adrenal atrophy mediated through inhibition of endogenous ACTH (Ingle 1938) Conversely patients with Addison s disease who have reduced or absent blood steroid levels exhibit increased amounts of ACTH in the plasma (Taylor *et al* 1949 Paris *et al* 1954 and others) The second or neurohumoral mechanism has been extensively studied by Harris and his group Hume Porter McCann Munson and Briggs and Guillemin (1950–1958) In brief the organism is presumed to react to a stimulus by activation of hypothalamic centers which in turn may secrete a neurohumor into the hypophysial venous portal system This material is carried to the adenohypophysis where it induces release of corticotrophin The nature of the postulated neurohumor is unknown but there is evidence suggesting that it is not histamine serotonin vasopressin or epinephrine (reviewed by Jailer and Christy 1957)

The physiological role of corticotrophin is implicit in the foregoing discussion Its function is to maintain the morphological and secretory integrity of the adrenal cortex A wide variety of noxious stimuli are associated in man with increased output of adrenal cortical steroids and by inference with an increased rate of endogenous ACTH release These stimuli include acute and chronic illnesses of several types (Perkoff 1954) *typhoid vaccine (Conn 1954) in*sulin hypoglycemia (Migeon 1953) stressful interviews and subacute emotional disturbances Direct assay for adrenocorticotrophin is difficult but no intrinsic defect of corticotrophin secretion or of the pituitary adrenal system has been conclusively shown in those systemic diseases ameliorated by ACTH or cortisone The relation between this hormonally mediated improvement and Selye s concept of an etiological or pathogenetic maladaptation to nonspecific stress remains controversial

In man administration of ACTH causes hyperemia and adrenal enlargement (especially of the zona fasciculata) Studies of adrenal vein blood have shown that the chief secretory products of the ACTH stimulated adrenal gland of man are hydrocortisone (compound F of Kendall) and corticosterone (compound B) (Bush and Sandberg Romanoff *et al* 1953) Only minor increments in aldosterone secretion have been produced by ACTH administration (Gordon) Haynes (1957) has shown that increased steroidogenesis is a result of increased synthesis and not of augmented

release Clinical measurement of plasma and urinary 17 hydroxycorticosteroid levels shows elevations during and for a few hours following ACTH administration (Nelson Samuels *et al* 1952–1955 and others) Detailed identification of urinary steroids following ACTH has shown increases in 11 desoxy and 11-oxy 17 ketosteroids the latter being end products of hydrocortisone metabolism (Gallagher *et al* 1955) increased amounts of C–21 metabolites of hydrocortisone (*e g* tetrahydrocortisone cortol) and the emergence of 11 desoxy hydrocortisone (compound S of Reichstein) (Touchstone 1955–1956)

The physiological effects of ACTH in man are in essence those produced by cortisone or hydrocortisone administration—an expected consequence of the finding that hydrocortisone is the steroid the production of which is most augmented by corticotrophin In theory minor differences between ACTH and hydrocortisone effects might be explained by the ACTH induced increment in corticosterone a fairly potent mineralocorticoid Certainly there are no differences compelling the use of cortocotrophin which must be injected when virtually the same effects can be achieved with steroids which may be given by mouth The well known effects of ACTH and hydrocortisone upon carbohydrate protein and sodium metabolism upon muscle function and the central nervous system and their androgenic effects do not provide hints as to how these hormones ameliorate disease The inhibitory influence exerted upon tissue response to injury (Ragan *et al* 1950) and upon antibody formation (Bjørneboe *et al* 1951) may by analogy furnish a basis for understanding the beneficial effects upon inflammatory and hypersensitivity disorders

ACTH is also capable of producing all the side effects of the adrenal steroids Prolonged administration is associated with the stigmata of Cushing s syndrome (hypertension osteoporosis occasionally glycosuria psychosis and so forth)

Although as stated above there is little reason to administer ACTH therapeutically over a prolonged period when steroids will do as well corticotrophin has found wide use in preventing symptoms of hypocorticism which result from long term steroid therapy with its accompanying adrenal atrophy It is probable that ACTH administration will accelerate return of adrenal weight and of adrenal response to ACTH toward normal However there has never been rigorous experimental proof that ACTH therapy can accelerate return to normal of endogenous pituitary response to stress It can therefore be argued that gradual steroid withdrawal may allow as rapid a restoration of a normal pituitary adrenal relationship as does ACTH therapy for a period of a few days

Chorionic Gonadotrophin The placentas of several species constitute temporary but important organs of internal secretion with gonadotrophic properties so nearly like those of the anterior lobe that brief if incomplete notation must be given here Chorionic gonadotrophin is apparently a glycoprotein arising from the human placenta and excreted in the urine It gives the classic Aschheim Zondek test for pregnancy by its gonadotrophic properties in immature mice and the Friedman test by its capacity to evoke ovulation in the rabbit in heat It is others) It does not produce follicular excreted in large amounts by men with testicular tumors (chorionepithelioma and growth in the ovary of the hypophysectomized rodent differing thereby from pituitary and castrate urine factors It is a powerful agent in protracting the life and function of the normal corpus luteum in women and in exciting androgen secretion in men with responsive testes Its real usefulness in correcting disorders of the menstrual cycle is uncertain

Pregnant Mare s Serum Gonadotrophin This is a protein with both follicle stimulating and luteinizing properties It produces antihormones readily in man in contrast to human chorionic gonadotrophin Its usefulness and effectiveness in man is a matter of disagreement

Hyperpituitarism

ACROMEGALY AND GIGANTISM

Definitions Acromegaly is a chronic disease characterized essentially by the progressive and systematic overgrowth of many tissues in response to intense and long sustained stimulation by the growth hormone of the pituitary body Other hormones may well cause certain expressions of the disorder although they are not now known to promote the characteristic overgrowth The name "acromegaly" (Marie 1886) designates the striking and presenting enlargement of the acral or terminal portions of the body the hands feet and certain elements of the face and head Gigantism appears not surely a clinical entity Some half



Fig 75 Roentgenogram of skull of an acromegalic with verified eosinophile adenoma of the hypophysis Note the ballooned sella turcica thick skull large frontal sinus and large mandible

or more of the recorded giants are acromegalic Here the youthful epiphyseal cartilages of the long bones proliferate in response to the excess of growth hormone a process favored by any influence such as gonadal insufficiency which delays their ossification A serious re-examination of etiology is required in those giants in whom no vestige of acromegalization ever occurs Constitutional factors apart from endocrine influences may be important forming a counterpart to the group of primordial dwarfs at the other end of the scale of size

Etiology Acromegaly and that form of gigantism properly associated with it are due to hypersecretion of the growth hormone from abundant neoplastic or hyperplastic cells of the anterior lobe of the pituitary body The excess of growth hormone provoking the dominant expressions of the disorder may be considered coming from these cells Since Bende s observation (1900) eosinophils or alpha cells have been held responsible although recently (Russfield 1956) "amphophiles have been spoken of—a suggestion of still uncertain fate Adenomas are most frequently described in autopsy or surgical material although diffuse hyperplasia may occur Over one half of the patients with acromegaly trace the onset to the third decade No useful theory accounting for this timing has appeared The sexes are affected equally although gigantism affects males chiefly Only 40 per cent of acromegalics give a history of similarly affected family members although in 20 per cent some note is made of large relatives (Davidoff 1926) A hereditary predisposition to diabetes mellitus as a complication seems clearer (Coggeshall and Root 1940)

The Pituitary Body and Its Environs The pituitary is usually large and the proliferative process considered adenomatous although hyperplasia occurs on occasion Although cellular aberrations are common with multinucleate cells and amitotic division and the term carcinoma has been applied in some instances metastases are rare Spread is largely by direct extension of the main tumor mass Eosinophils (acidophils alpha cells) typically dominate the cellular population Granulation however may be sparse and faint staining with the periodic acid Schiff reagent may be seen in contrast to the lack of such staining in the typical eosinophil Transition forms between eosinophil and chromophobe tumors have long been known and should be given a somewhat different meaning than that which the rather casual statements of the past implied Electron microscopy (Reichert 1954) shows many granules in chromophobe cells of normal human pituitaries not easily detected by stains A number of active tumors in man show little granulation Some of these have caused relatively indistinct forms of acromegaly others now are known to induce a syndrome with persistent lactation and amenorrhea signs which merge into those associated with acromegaly others still may be associated with Cushing s syndrome It is of especial interest in this connection that the highly active pituitary tumors of mice studied by Furth (1953–1958) often show little of the familiar granulation There still remain then some engaging mysteries in the relationships between cytological detail and the functional expressions of pituitary tumors

The growth of the tumor is typically slow and progressive The sella turcica is visibly distended in the majority of instances and assumes a ballooned appearance from pressure within its confines (Fig 75) The average adult sella turcica measured by roentgenogram is 8 to 9 mm in depth and 9 to 10 mm in length Upper normal limits are variously given as 10 to 12 and 12 to 16 mm respectively

These limits are usually but not necessarily substantially exceeded The floor of the sella is commonly depressed and the sphenoid cells may even be invaded At first the dorsum sellae is displaced back

wards Together with the clinoid processes it may eventually be eroded and destroyed The diaphragma sellae is forced upwards and may be ruptured Pressure is thus exerted upon the overlying optic chiasm and neighboring portions of the optic system A number of other cerebral areas come to express damage in their own particular ways

The tumor may appear stationary for years accommodations to existing pressure may take place and secretory activity may decline into relative quiescence Thus a stage of arrest which may last for almost any length of time supervenes Irregularly phasic activity may recur from time to time

Symptoms, Signs and Course The outward appearance of the well advanced acromegalic conforms as a rule to a single easily recognized type There is thickening and coarsening of the features notably of the lips and nose with accentuation of the normal eminences of the brow nose and lower jaw Mandibular prognathism is characteristic The hands and feet are large the thoracic cage increased in size the back stooped These deformities are exaggerations of familiar normal variations of man The continued growth of connective tissue and bone traverses the path from the not remarkable through the merely peculiar to the obviously deformed so slowly and by such imperceptible gradations that the early phases escape identification by the expert Even the later phases may seem right and proper though unusual to the patient and his family In gigantism accelerated longitudinal growth commonly appears in late boyhood and lasts longer than usual The typical stigmata of acromegaly are superimposed in due time



Fig 76 Acromegaly A and B Note the large and elongated head large hand nose ears and lips There is also prognathism and slightly increased interdental spaces C Note the coarse features D Large blunt pointed thumb (R H Williams Textbook of Endocrinology)

As this massive appearance emerges a contrasting enfeeblement afflicts the victim The disabilities are numerous Muscular weakness is eventually the rule although accounts of considerable early vigor are given Amenorrhea or impotence commonly occurs Excessive sweating is common *Diabetes mellitus supervenes in some* 15 per cent or more The hypertrophied and distended extremities may be painfully uncomfortable the affected joints of the extremities and spine stiff and painful Pain of neuritic character may occur The expansion of the tumor against the bony and ligamentous investments of the sella produces headaches which may be referred to the temporal area or elsewhere and which may be intense and continuous enough to disturb sleep One the other hand the pain may be transient or even insignificant As a result of pressure *visual difficulties* progressing to blindness are common Most typically the focus of pressure bears anteriorly impairing conduction in the decussating nasal nerve elements yielding bitemporal hemianopsia with initial upper quadrant defects Color vision is affected before form vision Many varieties of visual defects occur however with blindness only in the affected eye and homonymous hemianopsia among them Choked disk is rare As the growth extends the brain suffers from direct encroachment of the tumor from displacement and from obstruction to the ventricular systems *Drowsiness polydipsia* and *polyuria* may signify injury to the hypothalamus Usually after years of illness death comes from the brain tumor from cardiac failure from diabetes intercurrent disease or ultimate hypopituitarism The course is subject to great variations and long or even permanent remissions can occur leaving the *structural changes to mark the hormonal influences* of the past

Hormonal Influences on Structure and Function The greater part of the general somatic expressions of the disease are due to excessive secretion of the growth hormone of the pituitary body Chondrogenesis is stimulated with manifold consequences Increased proliferation of youthful epiphyseal cartilage elongates bones Gonadal defect secondary to the pituitary disorder diminishes androgens and estrogens Since these sex hormones tend to favor the ossification of the cartilages of the long bones continued growth is favored by their lack In the adult residual cartilage responds to stimulation The costal cartilages hypertrophy thus contributing decisively to the *enlargement of the thorax* a special form of arthritis follows proliferation of the deeper layers of joint cartilage growth of nasal and ear cartilages contributes to the acromegalization of the face and hypertrophy of the laryngeal cartilages makes for a *deep* and *husky voice* Osteogenesis succeeds chondrogenesis in gigantic overgrowth Osteogenesis from periosteum is greatly accelerated but so accompanied by resorptive processes that systematic alteration in shape is accomplished and the enlarged bones may come to be rarified rather than condensed Although the skull may be thickened generally with expansion of the diploic portion the frontal bone especially grows with protrusion of the supraciliary ridges and extraordinary excavation of the frontal sinuses beneath The ramus of the mandible extends and the angle is blunted thus advancing the lower jaw in the classic *mandibular prognathism* Heaping of new alveolar bone separates the teeth The bones of the hands and feet may be enlarged with *tufting of the terminal phalanges* The vertebrae may come to be virtually enclosed by shells of new bone Points of ligamentous and muscular insertions generally are accentuated by ossification within or about the attached structures the ligamentous apparatus of the spine especially becoming affected

Despite this extensive growth of bone the actual enlargement of the body members is commonly due chiefly to proliferation of the soft parts and in certain acromegalics it may be difficult to prove exceptional bone growth at all The true skin thickens and considerable *hypertrichosis* is common The sweat gland mass has been reported increased Connective tissue in the skin and in the subcutaneous and submucosal regions grows in excess giving the *large broad hands and feet* and the full lips and nose increasing the flaccid cutaneous structures about the eyes and producing the thickened corrugated "bull-dog scalp Hypertrophy of the soft parts about joints and fiber proliferation here and in the cartilage contribute to the arthritis The *tongue* is often large with great hypertrophy of the papillae Internal structures share the growth of these external and supporting tissues The *liver* may be twice or more the normal size and the lungs spleen pancreas and intestines enlarged Grafflin s account based on a model reconstruction shows that renal growth depends on hypertrophy of individual nephrons The *heart* may weigh as much as 1 kilogram more than three times normal with varying

growth and fragmentation of individual muscle fibers It is uncertain whether circulatory demand is sufficient to account for cardiac growth by work hypertrophy and a primary influence of the growth hormone on the cardiac musculature may be involved Skeletal muscle may respond for a time but progressive hypertrophy to a striking degree is not conspicuous Asboe Hansen has noted deposition of metachromatic material in the musculature similar to that induced by thyrotrophin The brain does not itself grow although perineurium about peripheral nerves does proliferate and certain ganglia have been reported enlarged

Experimental research leaves little doubt that the associated growth of skeleton connective tissue and viscera is due to the secretion of abnormal amounts of a single growth hormone Similarly thymic hypertrophy known in acromegaly since Fritsche and Klebs (1884) appears due to excesses of the growth hormone The frequent diabetes may well be due to the growth hormone This diabetes is variable in intensity may or may not require large amounts of insulin for control and may undergo spontaneous remissions Pituitary extracts rich in the growth factor exert influences on carbohydrate metabolism opposed to those of insulin and create a strain upon the islet mechanism Randle (1954) has found an excess of a factor in the plasma of acromegalics which enhances the uptake of glucose by the diaphragm of the rat in the manner of insulin The capacity of the patient s pancreas to secrete insulin would determine whether or not diabetes will ensue Ultimate degeneration of the islets analogous to that in dogs or cats (Young s or metahypophysial diabetes) may conceivably occur but has not been established at autopsy

Several other characteristics of the disease are less clearly due to excesses of the growth hormone or cannot be so accounted for at all The *basal metabolism* is commonly increased to plus 15 or 25 or more This contributes to the excessive sweating but is probably not a sole and necessary cause *Exophthalmos* may occur These features together with tachycardia and goiter may combine strongly to suggest complicating Graves disease directing treatment toward the thyroid and suggesting excessive thyrotrophin as a factor in pathogenesis Though Graves disease certainly is present at times the signs and symptoms suggesting it may often be misleading Dissociation of these signs and symptoms is common the goiters are often large and of a nodular colloid type and thyroidectomy or the use of antithyroid drugs may prove disappointing Although assays for thyrotrophin have been found elevated no correlation exists between this elevation and expressions of hyperthyroidism

Vascular hypertension may occur in cases of long standing and may in part be due to sclerosis of small vessels although the matter has not been carefully studied and other factors may enter in

The participation of ACTH in the process of acromegaly is uncertain Although moderate overgrowth of the adrenal cortex is common studies of urinary 17 ketosteroids have not given high results and the typical clinical expressions of Cushing s syndrome are rarely intermixed with acromegalization The hypertrichosis of acromegaly may be due to the growth hormone itself Since adrenal hormones appear to be antagonists to the anabolic effects of the growth hormone on protein metabolism a case could be made out for their reactive and compensatory hypersecretion Both plasma corticotrophin and urinary corticoids have been found elevated on occasion

The *excessive lactation* in acromegalic women may or may not have to do with prolactin The growth hormone itself may contribute

The *gonadal defects* in acromegaly and gigantism are presumably due to secondary damage to gonadotrophic elements of the pituitary itself either by pressure from the tumor or by involution in some subtle consequence of eosinophil proliferation No direct damaging effects of the growth hormone on the gonads are known with the better extracts The occasional complicating myxedema may be interpreted along similar lines Manifest general hypopituitarism may be an end result of exhaustion of the secretory elements and of their destruction by pressure and necrosis but this time honored concept could well stand modern documentation

Diagnosis A firm grasp of the clinical expressions of acromegaly is usually adequate preparation for recognition of the disorder The appearance in the advanced stages is pathognomonic but its early recognition may be difficult and in some cases time alone may tell A documented history of progressive and unusual increases in size is important increasing shoe and glove size or the imperfect fit of old rings may be suggestive Photographic records of changing features are most useful On occasion the fullness of the lips and tongue the

huskiness of the voice and puffiness about the eyes suggest myxedema but the pallor loss of head and body hair dryness of the skin and depressed heat production characteristic of hypothyroidism are usually absent in acromegaly Paresthesias and pains about the joints and elsewhere may be considered rheumatic or arthritic and the headaches may be wrongly assigned to that vast obscure category of functional headaches including migraine Roentgenograms of the skull usually but by no means always show typical excavation and enlargement of the sella turcica by the time the signs and symptoms cause concern Later perimetric studies of the visual fields may show distortion from pressure first in color fields later in those for form

Measurements of the secretory activity of the adenoma are indirect and imperfect Albright has suggested that increases in serum inorganic phosphorus may serve to indicate excesses of the growth hormone The method has experimental support and may well prove useful The basal metabolic rate may be normal or elevated Diabetic glucose tolerance curves or frank diabetes mellitus usually speak for hyperactivity particularly if accompanied by any notable insulin resistance Serial evaluations of secretory activity x rays of the sella visual studies and neurological examinations are essential for years once the disorder is established for the appraisal of activity of the disease process

Treatment In embarking upon treatment it is necessary to judge the size of any existing pituitary adenoma and its rate of growth to estimate the secretory activity at the time and to assess the extent of damage to the visual pathways and the brain

Irradiation of the pituitary body by x rays is preferred More intensive radiation than hitherto used has been recommended by Johnsen (1952) Arrest of the process often occurs as judged by improvement in the visual fields headache and in signs of secretory activity The imperfections of measurements and the exceedingly slow and variable course of the disease itself make evaluation difficult Albright has recommended the use of large doses of diethyl stilbestrol based on the capacity of estrogens in experimental animals to deplete the anterior lobe of eosinophils and to retard growth Depression of serum inorganic phosphorus suggested reduction in growth hormone secretion but the eventual course of the tumors remains uncertain Surgical removal of the adenoma is commonly reserved for those whose sight is threatened but the current advancements in extirpation and destruction of the hypophysis may well extend the usefulness of these procedures in acromegaly As it stands now all methods may fail and smoldering residual activity may prevail with lingering disability of varying degrees

Associations of Acromegaly and Other Syndromes Tumors of the pituitary body inducing acromegaly may be associated with functioning endocrine tumors elsewhere notably with parathyroid and islet cell adenomas of the pancreas (Wermer 1954) the syndrome being called *endocrine adenomatosis* The signs of these disorders should be watched for Chromophobe tumors not inducing hyperpituitarism may be similarly associated (Underdahl *et al* 1953) As noted earlier there is a gradation between granule bearing and non granule bearing tumor cells and cells giving evidence of functional activity may be termed chromophobe Some of these are associated with galactorrhea and amenorrhea (Forbes *et al* 1954) The excretion of urinary gonadotrophins appears reduced Such excessive lactation may appear in acromegaly and there is a reasonable disposition to assign the galactorrhea in both instances to excesses of prolactin The writer is not certain that this has been demonstrated the rather difficult view that there is an inhibitory or destructive action may have to be entertained Similarly tumors which are chromophobe or basophile may be associated with Cushing's syndrome and the issue of excessive secretion of adrenocorticotrophin arises

CUSHING S SYNDROME

See the discussion under Diseases of the Adrenal Glands

PRECOCIOUS PUBERTY

See section on Diseases of the Sex Glands

Hypopituitarism

The greater part of our clinical information deals with gross destructive lesions of the pituitary body causing numerous defects Isolated impairment of the capacity of the anterior lobe to make one hormone or a group of hormones leaving the remainder of its functions intact is poorly understood for the most part and imper

fectly documented In a number of eunuchoids without obvious general defects of pituitary origin urinary assays for gonadotrophin are low and androgen secretion in response to chorionic gonadtrophin may be substantiated This provides excellent evidence for a relatively isolated pituitary deficiency affecting the entire gonadotrophic complex Disorders affecting other functions are emerging (Myers *et al* 1953) although uncertainty still exists as to whether or not these are the predominant and prevailing expressions of a gross lesion or whether a single cell line has suffered from some peculiar intrinsic defect

A form of isolated adrenocorticotrophin deficiency may occur when corticoids are suddenly withdrawn Fever prostration and vascular collapse of adrenal insufficiency ensue

SIMMONDS DISEASE

(*Panhypopituitarism*)

Definition Primary chronic hypopituitarism involves defects in several pituitary functions leading usually to more or less general disability Usage of the term and the criteria for nomenclature are confused for historical reasons

History Simmonds (1914) described an autopsy on a woman with a history of puerperal sepsis and noted cachexia with loss of weight and atrophy of the skin loss of pubic hair amenorrhea and splanchnomicria He attributed the fibrosed pituitary body to septic embolism years before He adopted the term "pituitary cachexia" emphasized cachexia as a cardinal feature and subsequently pointed out that similar clinical states followed damage to the anterior lobe from other causes including tumors Subsequent authors continued this emphasis on cachexia often meaning excessive weight loss although brain surgeons including Cushing for years recognized a related state of geroderma weakness loss of pubic hair and sexual defects in the victims of chromophobe adenomas of the pituitary body who might or might not have lost much weight The emphasis on weight loss has led to the confusion of primary pituitary disease (called Simmonds disease or pituitary cachexia) with anorexia nervosa in certain quarters Sheehan (1937–1949) has done much to straighten matters out His major contributions have rested on his detailed description of fresh infarcts in the anterior lobes of women dying from collapse and hemorrhage at childbirth relating these to the ultimate fibrosis described by Simmonds and others in those who survived such injuries and pointing out that cachexia in the sense of weight loss was a relatively infrequent expression of the disease He suggested postpartum necrosis for the lesions arising at childbirth but retained the name of Simmonds disease for severe hypopituitarism of whatever origin This work brought the general clinical consequences of postpartum necrosis close to experience with pituitary tumors Albright s term "panhypopituitarism has had considerable appeal and is appropriate when used to mean what it says The writer will use the more noncommittal Simmonds disease" in Sheehan s sense but the reader must expect a continuing change in terminology as knowledge grows and conventions shift

Etiology and Pathology Postpartum necrosis of the anterior lobe of the pituitary body is common in women dying from collapse or hemorrhage at childbirth These infarcts which may be tiny to nearly total have been attributed by Sheehan (1937) to local thrombosis rather than to septic embolism (Simmonds 1914) Strands of viable tissue often survive near the attachment of the stalk or along the capsule Fibrosis supervenes and years later contracted shreds of anterior lobe tissue may be found in those surviving such obstetric accidents Direct damage to the pituitary body may occur following head injuries hemorrhage into its substance being presumably decisive Granulomas may occur and have been attributed to tuberculosis rarely to syphilis Fibrosis of a diffuse type distinguishable from the more sharply demarcated scars of infarction has been noted in both sexes since Claude and Gougerot (1908) and is of obscure origin although thought syphilitic by some

Tumors arising either within or outside the sella may compress and destroy the pituitary body Of those arising within chromophobe adenomas are the most common Developing from stem cells of the secretory elements of the anterior lobe they are nonfunctioning save for rare and sparse granulation which may be associated with some degree of activity Endocrine symptoms are therefore produced largely by impairment of the secretory elements The sella is ballooned the clinoid process eroded the visual system encroached upon and the brain invaded much as in the eosinophile adenomas described under Acromegaly

Craniopharyngiomas (a term not universally accepted) also known as Rathke pouch tumors arise from fragments of the oral epithelium remaining from the primitive invagination Although intrasellar on rare occasions they are more likely to proliferate from the neighborhood of the upper suprasellar reaches of the stalk They give symptoms often during childhood in contrast to chromophobe adenomas which typically begin during adult life Comprised chiefly of oral epithelium often with squamous cells or important dental elements (adamantinoma) these tumors show a strong disposition to necrosis and cyst formation with points of calcification which may be recognized on roentgenograms The sella is likely to be stretched anteroposteriorly with ero

sion of the clinoids rather than first ballooned as with primarily intrasellar lesions and the visual system is often affected early and irregularly The brain is slowly distorted by progressive growth and hypothalamic symptoms are common Neurological texts should be consulted for a discussion of other intracranial tumors which must be distinguished from craniopharyngiomas and which may produce similar damage directly or indirectly

With gross injury to the hypophysis of whatever origin the gonads adrenal cortex and thyroid glands are likely to show atrophic changes and the liver and other viscera to be small (splanchnomicria) in contrast to the splanchnomegaly seen in acromegaly

Symptoms, Signs and Course The appearance of the various signs and symptoms depends in part upon the size of the lesion and the rate of its development Ordinarily gonadal deficiencies occur most readily those of the thyroid and adrenal cortex in succession thereafter Animal experiments have recently suggested that this sequence not invariable is more nearly related to progressive destruction of greater and greater amounts of pituitary tissue than to sequential injury of specific areas in the gland (Ganong and Hume) Thus after postpartum necrosis the menses may not return With chromophobe adenomas amenorrhea is often the first stigma The atrophy of the gonads and secondarily of the genitalia is profound in any severe grade of hypopituitarism As judged in children growth deficits occur relatively easily In adults the margins of safety within the gland for growth hormone production are hard to judge Hypoglycemia may occur at the time of postpartum necrosis may lead to coma and may urgently require the use of glucose in treatment

Atrophy of the skin is common There is infantile smoothness dryness and a fine wrinkling which when extreme gives that appearance of precocious aging (geroderma) that so struck Simmonds The subcutaneous fat is usually well preserved although on occasion when weight loss is great it may largely disappear Body hair is usually reduced and loss of pubic hair the beard and axillary hair given time and a severe lesion is common and of diagnostic significance These atrophic skin changes are partly due to reduction in androgen secretion although the role of loss of the growth hormone is not clear The skin is rarely puffy as in myxedema despite the commonly reduced basal heat production which may reach levels as low as minus 40 for long periods Rarely however typical myxedema appears (*pituitary myxedema*) Radio-iodine uptake by the thyroid gland and serum precipitable iodine are decreased These indicators however may not be as much depressed as in primary hypothyroidism nor is the serum cholesterol as consistently elevated It is likely that residual thyroid activity remains in man as in lower forms after destruction of the hypophysis

The skin is commonly pale with a faint yellowish cast occasionally but by no means always due in part to a normocytic anemia and tans poorly Even with manifest suprarenal deficiency Addisonian pigmentation does not occur It is now apparent that a melanocyte stimulating hormone (or hormones) secreted by the pituitary body and detectable in serum and urine is present in excess when the adrenal is directly damaged (Sulman 1952 Lerner and Takakashi 1956) This agent when given to man darkens the skin (Lerner) It may represent either an intermediate lobe secretion or the action of the melanocyte stimulating moiety of the ACTH molecules In any event the effective hormone can no longer be secreted in excess in response to whatever adrenal cortical deficit results from pituitary failure

Weakness and loss of energy to the point of incompetence and mental apathy are common although on occasion performance is amazingly good despite substantial endocrine deficits Psychoses may occur Hypotension is often present with orthostatic exaggeration and syncope may occur Water diuresis is slow little or no increase of urine volume occurring in 4 hours after the ingestion of a liter or more of water Excesses of water readily induce water intoxication Though adrenal cortical defects contribute to these peculiarities outstanding adrenal insufficiency is not regularly present Abnormalities in the concentration of serum electrolytes typical of Addison s disease are not usually seen In the studies after hypophysectomy for cancer it has been noted that even salt restriction may be well tolerated (Lipsett *et al* 1957) The adrenal cortex continues to secrete aldosterone in the absence of the pituitary body and can increase this secretion when needed Reduction in urinary sodium and chloride excretion results (Luetscher *et al* 1956 Maclean *et al* 1957) In long standing pituitary disease aldosterone secretion may be less than adequate and weakness and hyponatremia fol

low salt restriction (Luetscher 1956) It is likely that the aldosterone secreting mechanism requires a degree of anterior lobe sustenance in the long run Excesses of urinary sodium and chloride after salt restriction as in true Addison s disease (Loeb 1933) may well occur although Lipsett Pearson *et al* have found the earlier data in hypopituitarism defective and noted that water intoxication alone may cause hyponatremia and weakness Save for these peculiarities in the behavior of sodium chloride and potassium the adrenal crises of hypopituitarism are much like those of Addison s disease They are characterized by anorexia nausea and vomiting prostration hypotension and fever They may occur spontaneously or may be precipitated by stress or by the sudden withdrawal of cortisone The activity of the thyroid hormone predisposes to adrenal incompetence

Urinary corticoids are characteristically low in hypopituitarism Urinary 17 ketosteroids may be low or virtually absent depending on the duration and extent of the adrenal and gonadal (testicular) defect Hypoglycemia may be troublesome emerging especially after prolonged fasting and is often readily induced by small doses of insulin This latter procedure is dangerous As previously noted both the growth hormone and the adrenal steroid or steroids governed by adrenocorticotrophin contribute to the control of carbohydrate metabolism and to opposition to insulin It is not always clear how much loss of each contributes to the defects of hypopituitarism

Anorexia to some degree is common but the metabolic requirements are low and conspicuous loss of weight may not occur More rarely loss of weight is substantial and contributes an important element to an appearance of cachexia Progressive obesity is rare in hypopituitarism alone and bespeaks hypothalamic injury when it does occur (see Frohlich s Syndrome)

With tumors the endocrine aspects may be completely dominated by the mechanical effects of the neoplasm and reduction in visual acuity to blindness headache and the various other expressions of an expanding intracranial lesion come to preoccupy the patient and to demand concentrated attention

Diagnosis * The milder forms of hypopituitarism are most likely to escape detection The history of obstetric accident with collapse or hemorrhage points to the possibility of postpartum necrosis and should always be sought Anorexia nervosa affects chiefly young females and the considerable emaciation the maintenance or increase of body hair the restless behavior and the manifest emotional disorder form a general clinical picture usually quite distinct from that of Simmonds disease Genuinely retarded sexual development in either sex requires investigation of the possibility of gross pituitary disease Amenorrhea in women of previously normal menstrual habit should lead to consideration of gross pituitary disease and the presence of fine hairless skin with reduction or loss of axillary or pubic hair is especially suggestive Films of the sella usually show distinct ballooning and enlargement if a chromophobe adenoma is responsible Calcification in the region of the sella suggests the possibility of a craniopharyngioma Urinary gonadotrophin studies may be helpful since the values are high in early natural menopause low in primary pituitary disease

With adequate clinical or radiological evidence of pituitary disease distinctions can readily be made between primary thyroid and adrenal insufficiency and the deficiencies of these glands which ensue from hypophysial failure Without such aids (there are many pituitary lesions which do not cause sellar enlargement) differentiation may be extremely difficult Primary adrenal insufficiency Addison s disease is usually associated with increased pigmentation of the skin which is rarely if ever present in the secondary adrenal insufficiency of hypopituitarism A logical basis for this difference is provided by the demonstration of increased blood concentrations of melanocyte stimulating hormone (MSH) in patients with primary adrenal cortical failure in whom the normal inhibitor of ACTH and MSH secretion by the pituitary is lacking (Lerner Sulman) In contrast patients with Simmonds disease may be supposed to have a relative deficiency of MSH indeed they often exhibit a pallor out of proportion to the moderate degree of anemia usually present The difficult problem in Simmonds disease is to establish with certainty whether or not secondary adrenal insufficiency exists This is of obvious importance in planning replacement therapy Low urinary steroid excretion values are the rule in patients with hypopituitarism but this abnormality may be due in part to reduced thyroid and gonadal function and to the poorly understood changes brought about by a chronic debilitating disease Testing with adrenocorticotrophin has been used in several clinics Infusion of 25 U S P units intravenously over

* Revised by Dr Nicholas P Christy

periods of four to eight hours may be expected to induce subnormal but definite increases in urinary and plasma 17 hydroxycorticosteroids and depression in the concentration of blood eosinophils below 50 per cent of the original value If the atrophy due to pituitary defect is of long standing repeated stimulation may be required before a response is secured In primary adrenal cortical insufficiency *i e* Addison s disease there is usually no steroidal response to repeated ACTH testing which may partly account for the frequency of allergic reactions to corticotrophin in the Addisonian patient and for the occasional precipitation of adrenal crises in this group In general this procedure should be used with caution if at all in those with pituitary disease to assess the state of the adrenals and should be avoided in primary adrenal disease Other provocative tests such as salt withdrawal water loading and tolerance to insulin may be abnormal in both primary and secondary adrenal cortical failure and in primary hypothyroidism They are therefore of limited differential diagnostic value and may be dangerous to the hypopituitary subject As an index of the integrity of the pituitary adrenal system eosinophil response to epinephrine is of uncertain validity (Thorn) especially in view of the demonstration that this amine does not cause increased adrenal cortical secretion in man (Sandberg *et al*)

In thyroid deficiency secondary to pituitary failure the patient typically presents the depressed basal metabolic rate of hypothyroidism without the soft tissue swellings of myxedema although skin lesions are microscopically identical in primary and secondary hypothyroid states Poor tolerance to thyroid in myxedema should lead to suspicion of anterior lobe deficiency and is probably caused by the associated adrenal defect On rare occasions however primary thyroid disease itself leads to adrenal deficit of clinical and anatomical significance and the cautious use of thyroid is beneficial rather than harmful Amenorrhea especially if genital atrophy is marked suggests hypopituitarism menorrhagia may suggest hypothyroidism Serum cholesterol levels tend to be lower in secondary than in primary hypothyroidism but in many instances of Simmonds disease concentrations of 300 to 600 mg per 100 ml are encountered Uptake of radioactive iodine is low as a rule but may for unknown reasons be normal in the face of clinical thyroid insufficiency and low levels of serum precipitable iodine Response of the thyroid to intramuscularly administered thyrotrophin (TSH) measured by increments in radioiodine uptake protein bound iodine or basal metabolic rate is suggestive of secondary hypothyroidism However atrophy of the thyroid due to pituitary defect of long standing may respond slowly to TSH as does the secondarily atrophied adrenal cortex to ACTH (*vide supra*) Available preparations of TSH appear to cause untoward reactions on occasion

It should be emphasized that the numerous tests alluded to above have limitations and are often attended by difficulties in execution and in interpretation They have their chief utility as adjuncts to not as substitutes for due attention to history and physical examination

Treatment Chromophobe adenomas may be less sensitive to irradiation than chromophile tumors but this therapy should be tried in the hope of arresting the process Craniopharyngiomas are still less sensitive Significant restoration of pituitary function is rare Progressive loss of vision despite irradiation or other evidences of continued intracranial expansion may require attempts at surgical reduction of the tumor mass By virtue of the location of the tumor the approach is difficult hazardous and often unsuccessful

The endocrine defects are best managed by substitution therapy for the dependent glands If the adrenal cortical defect is latent as is commonly the case both the wisdom and the usefulness of vigorous treatment may be considered sub judice at this time General well being is then the chief criterion of response and this is of course influenced by many factors including subjective ones When the adrenal insufficiency is manifest under ordinary living conditions the treatment corresponds to that for Addison s disease (see Addison s disease) Although sustained treatment with ACTH is feasible injections must be given daily and cortisone or hydrocortisone 12 5 to 50 mg daily in divided doses orally will usually be preferred Potassium deficits should be guarded against It must be remembered that cortisone will depress residual adrenal function so that the gain from treatment must be clear and any discontinuance gradual and guarded ACTH may be used to restore the depressed adrenal In manifest crises of adrenal insufficiency treatment corresponds to those of primary Addison s disease ACTH may be used to support and restore the adrenal cortex but it may not work quickly enough

if the adrenals have long been atrophic and should not be counted on as a sole measure Preparations of ACTH and their use are cited briefly under adrenocorticotrophin In general the patient with hypopituitarism should be protected against those events known to put a strain on the pituitary adrenal axis ACTH may serve from time to time to aid in this protection when the strain such as a surgical operation is unavoidable

Frequent feedings of carbohydrate in day to-day management and the use of intravenous glucose for emergencies may be essential for the control of hypoglycemia Cortisone may be expected to protect against such hypoglycemic episodes and to contribute to their control Thyroid may be helpful in sustained treatment but the reasonable integrity of the adrenal cortex should be assured or any deficiency provided for in advance Dosage should be small at first (6 mg to 15 mg daily) and increased slowly to 30 or perhaps 60 mg daily On rare occasions unexpected collapse apparently of adrenal origin may follow vigorous treatment with thyroid Androgens (testosterone propionate 25 mg two or three times weekly by injection methyl testosterone 20 to 50 mg daily orally perhaps somewhat less by linguets) may be used to enhance masculine secondary sex characteristics Although anabolic effects of protein metabolism are demonstrable opinion differs as to the general gain from such influences in adult Simmonds disease Interpretations of increased well being and strength are governed by subjective factors and are greatly affected by a complex metabolic situation While chorionic gonadotrophin would appear more elegant than androgens stimulating rather than replacing the testes its advantages do not appear real enough at this time Repair of sperm formation by this gonadotrophin has not been shown with any regularity It should not be forgotten that some patients are best left untreated if the external demands can be adjusted to their capacities

HYPOPITUITARISM DURING CHILDHOOD (INCLUDING ATELEIOSIS)

(Pituitary Dwarfism)

Gross pituitary defect arising during childhood is expressed by retardation of somatic growth in addition to the endocrine deficiencies previously cited This impairment of growth is relatively uniform throughout the skeletal visceral and cardiovascular systems yielding a small but relatively harmoniously developed person whose childish proportions and contours mark the time of growth arrest for years to come (Fig 77) The cartilaginous epiphyses remain unossified for long periods The secondary gonadal insufficiencies contribute in their own characteristic ways to the fixation of the sexual attributes of childhood Later the atrophic skin may be wrinkled superimposing an incongruous aspect of aging The profound impairment of the development and function of the central nervous system seen in cretinism does not occur nor does the myxedematous infiltration of the subcutaneous and submucous tissues so characteristic of juvenile myxedema appear to be frequent The several metabolic consequences of adrenal defect are less conspicuous than in Addison s disease and must be sought On occasion a pituitary tumor can be demonstrated more often perhaps careful physiologic studies will create a strong presumption for pituitary responsibility

Autopsy experience is limited Craniopharyngiomas are the most common tumor (see Etiology of Hypopituitarism) and are rarely intrasellar (Erdheim) Cysts of a developmental sort are known including those occurring between separated anterior and posterior lobe anlagen which remain in positions indicating arrest of embryologic processsion (Priesel) Simmonds noted fibrosis of unknown origin It is by no means clear that a full histological account of the real varieties of pituitary defect has been given and one misses descriptions of aplasia or hypoplasia of a pituitary cell line analogous to that in the hereditary dwarf mice of Smith and MacDowell Familial associations of growth defects are common in man

The establishment of diagnosis based on etiology is especially difficult when growth alone is defective sexual development normal and other endocrine disorders not conspicuous Such dwarfs are often termed primordial and held to be small but otherwise normal persons analogous to the pygmy races of man The term "constitutional is often used to imply a peripheral tissue growth defect than a primary pituitary disorder Though such interpretations are reasonable it must be recalled that neither autopsy experience nor assays for growth hormone nor measurements of response to growth hormone suffice now to place them beyond question Throughout the entire problem of dwarfism this interplay of tissue response and hormonal impetus is imperfectly understood The term

periods of four to eight hours may be expected to induce subnormal but definite increases in urinary and plasma 17 hydroxycorticosteroids and depression in the concentration of blood eosinophils below 50 per cent of the original value If the *atrophy due to pituitary defect is of long* standing repeated stimulation may be required before a response is secured In primary adrenal cortical insufficiency *i e* Addison s disease there is usually no steroidal response to repeated ACTH testing *which may partly account for the* frequency of allergic reactions to corticotrophin in the Addisonian patient and for the occasional precipitation of adrenal crises in this group In general this procedure should be used with caution if at all in *those with pituitary disease to* assess the state of the adrenals and should be avoided in primary adrenal disease Other provocative tests such as salt withdrawal water loading and tolerance to insulin may be abnormal in both primary and secondary adrenal cortical failure and in primary hypothyroidism They are therefore of limited differential diagnostic value and may be dangerous to the hypopituitary subject As an index of the integrity of the pituitary adrenal system eosinophil response to epinephrine is of uncertain validity (Thorn) especially in view of the demonstration that this amine does not cause increased adrenal cortical secretion in man (Sandberg *et al*)

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*It should be emphasized that the numer*ous tests alluded to above have limitations and are often attended by difficulties in execution and in interpretation They have their chief utility as adjuncts to not as substitutes for due attention to history and *physical examination*

Treatment Chromophobe adenomas may be less sensitive to irradiation than chromophile tumors but this therapy should be tried in the hope of arresting the process Craniopharyngiomas are still less sensitive *Significant restoration of pituitary function* is rare Progressive loss of vision despite irradiation or other evidences of continued intracranial expansion may require attempts at surgical reduction of the tumor mass By virtue of the location of the tumor the approach is difficult hazardous and often unsuccessful

The endocrine defects are best managed by substitution therapy for the dependent glands If the adrenal cortical defect is latent as is commonly the case both the wisdom and the usefulness of vigorous treatment may be considered sub judice at this time General well being is then the chief criterion of response and this is of course influenced by many factors including subjective ones When the adrenal insufficiency is manifest under ordinary living conditions the treatment corresponds to that for Addison s disease (see Addison s disease) Although sustained treatment with ACTH is feasible injections must be given daily and cortisone or hydrocortisone 12 5 to 50 mg daily in divided doses orally will usually be preferred Potassium deficits should be guarded against It must be remembered that cortisone will depress residual adrenal function so that the gain from treatment must be clear and any discontinuance gradual and guarded ACTH may be used to restore the depressed adrenal In manifest crises of adrenal insufficiency treatment corresponds to those of primary Addison s disease ACTH may be used to support and restore the adrenal cortex but it may not work quickly enough

in some cases before notable weight loss but with the onset of emotional disturbance suggests an interpretation analogous to that of the amenorrhea of psychoses The deficiency in gonadotrophin secretion is thus considered secondary in part to starvation and in part to disturbed mental state

The few autopsies have shown no gross or microscopic pituitary disease Clinical studies of endocrine function have usually yielded evidence of reduced hormonal activity but the obvious personality disorder generally renders the distinction from Simmonds disease easy Urinary estrogen levels are reportedly low and vaginal smear shows no cornified cells The basal metabolic rate is low often markedly so the serum cholesterol normal and thyroidal uptake of I^{131} normal Urinary 17 ketosteroid excretion tends to be reduced but ketosteroid rise after corticotrophin administration is normal In the recovered patients most of these indices of endocrine activity revert to normal

The disorder may develop after dieting for obesity The aversion to food is profound or if hunger is experienced satiety comes so quickly that eating provides little more than a nibbling of sweet insufficient juices perhaps enough to prevent ketosis but far from enough to meet energy requirements A variety of disagreeable abdominal sensations occurs including nausea Vomiting is common if food is forced and is often self induced The loss of weight is extreme often reducing the victim to the contours of her bony skeleton Unlike Simmonds disease however sexual hair is retained and even a fine general hypertrichosis may develop Despite her pitiable plight the victim is often active or restless with an even cheerful preoccupation with trivia Sustained effort is difficult and pressure especially to eat may lead to every variety of deceit to avoid compliance Moderate anemia hypoproteinemia and nutritional edema may develop Death may occur from starvation after years of debility

Treatment comprises reeducation of the patient with persuasion to eat together with whatever gentle force the physician can command Psychiatric care is desirable if judicious but the results are variable In a few hands they seem good indeed but great patience is necessary and failure is common enough Endocrine treatment has not been established as valuable

A T KENYON

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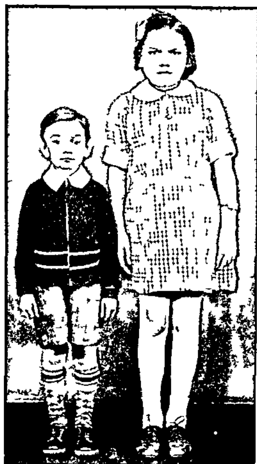


Fig 77 Two children of the same age The one on the right is normal The one on the left had a craniopharyngioma at the age of 5 Note the com plete cessation of growth

ateleiosis (Gilford) which is wisely non descript might well be reserved for the generality of dwarfs both with and without sexual defects until the extent of true hypo pituitarism in explanation can be fully ascertained

Primary pituitary disease in girls must be distinguished from the much more common association of shortness of stature with ovarian defect The associated variegated congenital anomalies often include the cu bitus valgus and webbed neck described by Turner (Turners syndrome) These sub jects show no evidence of hypopituitarism on detailed study and urinary gonadotro phins are high Studies recently initiated by Barr often show none of the typically female chromatin like bodies near the nu clear membrane of the cell The cells thus resemble those of males and the subjects have been interpreted as genetic males As no positive identification of masculine nuclei is possible now this interpretation is presumptive and should be held as a working hypothesis only (See the section on Diseases of the Sex Glands for further discussion)

The treatment of hypopituitarism in child hood is much the same as in adult life Some increase in stature may be expected from the use of androgens although full restoration of normal growth is not to be expected Use of androgens in the female must be carefully guarded

FRÖHLICH S SYNDROME

(Adiposogenital Dystrophy)

Since Frohlich s (1901) account of mild obesity and retardation of genital develop ment in a boy with the visual field defects of a pituitary tumor the association of obesity and hypogonadism has been termed Frohlich s syndrome although *adiposogeni tal dystrophy* is more precise Erdheims view that the progressive obesity is due to hypothalamic lesions rather than to hypo pituitarism has received modern experi mental support Excessive eating is the most important factor in producing this obesity Genital dystrophy has similarly been induced by circumscribed hypothal amic lesions but in this instance secondary hypopituitarism presumably occurs The term "Frohlich s syndrome" may be properly applied to the pituitary or juxtapituitary lesions in which the association of obesity and hypogonadism is due to a common cause Hypogonadism *per se* does not give rise to progressive obesity Obesity in chil dren before puberty should not be termed Frohlich s syndrome nor can hypopituitar ism be often held responsible for their obesity Obesity of hypothalamic origin will respond to dieting if appetite can be con trolled

ANOREXIA NERVOSA*

Anorexia nervosa is a chronic disorder chiefly of young women and is character ized essentially by an obsessive aversion to food leading to emaciation Amenorrhea is the rule Gull described the disease and at tributed it to a functional disorder of the nervous system an interpretation which survives The profound emotional and char acter disorder the tendency to develop with the assumption of independent adult life and the common history of grievous per sonal difficulties support this view together with the recovery that may be made under fortunate medical and general environ mental conditions The emotional disorder is held to be a neurosis with compulsive anxiety depressive and often schizophrenic features The early onset of the amenorrhea

* Revised by Dr Nicholas P Christy

Table 1 Relative Biological Potency of the Adrenocortical Steroids

	GLUCONEO-GENESIS	ANTI INSULIN	LIFE MAINTENANCE	SODIUM RETENTION	ANTI INFLAMMATORY	RENAL BLOOD FLOW	STRESS RESISTANCE
Natural Steroids							
Hydrocortisone and cortisone	++++	++++	+	+	++++	++++	++++
Corticosterone	++	++++	+	+	0	+	+
Desoxycorticosterone	0	+	++++	++++	0	+	0
Aldosterone	+	+	10–30 × DOCA	10–30 × DOCA	0	+	+
Synthetic Steroids							
Prednisone and prednisolone	5 × Hydrocortisone	5 × Hydrocortisone	++	0	5 × Hydrocortisone	5 × Hydrocortisone	5 × Hydrocortisone
6 Methyl prednisolone	10 × Hydrocortisone	10 × Hydrocortisone	+++	0	10 × Hydrocortisone	10 × Hydrocortisone	10 × Hydrocortisone
9α fluorohydrocortisone	++++	++++	5–10 × DOC	5–10 × DOC	++++	++++	++++

hydrocortisone and related compounds are very potent mineralocorticoids The latter steroids also have glucocorticoid activity but cannot be used as such since their salt retaining activity is so great as to overshadow their hydrocortisone like activity

Steroid Biogenesis With this array of known substances extractable from adrenal tissue the question has been debated whether one two three or all the steroids were secreted by the adrenal cortex However since the first demonstration by Bloch of the conversion of isotopically labeled cholesterol to progesterone in the pregnant woman and a series of studies by Hechter Pincus Dorfman Samuels and others on the mechanism of steroid synthesis within isolated adrenal tissue the riddle of the multitude of adrenal steroids seems closer to solution

Cholesterol is the major precursor in the formation of the adrenal steroids The first step in steroidal synthesis from cholesterol is the scission of the side chain resulting in the formation of Δ pregnenolone The next step is the conversion of Δ^5pregnenolone to progesterone by the action of the enzyme 3 β-ol hydrogenase Progesterone apparently is the mother steroid for the synthesis of the other hormones (Fig 79) Adrenal tissue contains a series of enzymes which can hydroxylate the progesterone molecule at the C 17 (17α hydroxy progesterone) C 21 (Compound S) and C 11 position in a steplike fashion and thus synthesizes hydrocortisone Aldosterone is probably synthesized from corticosterone It has also been demonstrated that testosterone may be derived from the cleavage of the 17α hydro progesterone side chain and can give rise to estradiol

These biochemical transformations can occur in the presence of cell free prepara

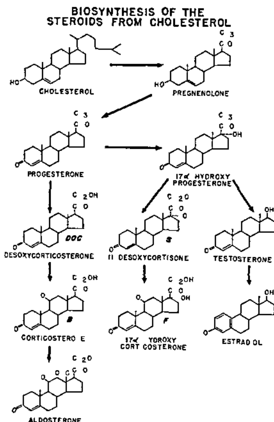


Fig 79

STEROID PHYSIOLOGY AND METABOLISM

Introduction In the relatively short time since the first steroidal hormone was isolated an impressive amount of information has been accumulated regarding the role of the adrenocortical and gonadal steroids in many bodily mechanisms The introduction of specific and sensitive analytical methods for the determination of steroids and their metabolites in biological fluids has furthered knowledge relative to the precise mechanism of synthesis within some of the endocrine glands The sum total of this investigative endeavor has produced basic information in this field which has helped explain many of the manifestations of adrenal diseases

Over forty different steroids have been isolated from adrenal tissue These steroids

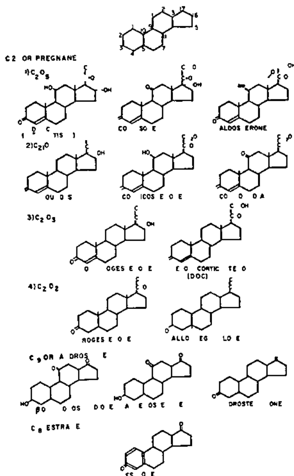


Fig 78 Steroids isolated from adrenal tissue

can be classified according to the number of carbon atoms in the molecule as is shown in Figure 78 The C 21 steroids are commonly referred to as corticoids and are pregnane derivatives they can be subdivided further according to the number of oxygen atoms The C 19 steroids are androgens or androstane derivatives The C 18 steroids are estrogens

The adrenal steroids may also be classified according to their physiological activity which to a degree is dependent upon the chemical structure (Table 1) The hormones isolated from adrenal tissue fall into five general biological categories These are (1) *The glucocorticoids hydrocortisone or cortisol and corticosterone* The important physiological effect of this class of adrenal steroids is to promote gluconeogenesis from the catabolism of protein They also inhibit the action of insulin Renal blood flow is increased by the administration of steroids of this class and they also protect adrenalectomized animals against stress Hydrocortisone and cortisone have a very potent anti inflammatory effect (2) *The mineralocorticoids aldosterone and desoxycorticosterone* Although these hormones are very effective in maintaining the life of adrenalectomized animals under ideal laboratory conditions they are not very effective in protecting against stress Their primary effect is to promote the retention of sodium and the excretion of potassium by the renal tubule (2) *Androgens androstenedione 11β OH androstandione* The function of these steroids is not clear although androstenedione is a very potent androgen having approximately one half the biological activity of testosterone (4) *Progesterone* and (5) *Estrone*

Other steroids which have been isolated from adrenal tissue are biologically inert and still others have been found in insufficient quantity for biological assay

In addition several new steroids have been synthesized which are somewhat different in chemical structure from the naturally occurring ones Prednisone prednisolone and 6 methyl prednisolone are powerful glucocorticoids whereas 9α fluoro-

lation comes from the acetate moiety There is however no complete agreement on this point

The Catabolism of the Steroids From analyses of human adrenal vein blood it has been established that the adrenal cortex secretes hydrocortisone corticosterone aldosterone and trace amounts of 11β OH androstenedione and Δ^4androstenedione (Although dehydroisoandrosterone has not been identified in adrenal vein blood it is the most abundant C 19 steroid found in peripheral blood) It is possible that under certain conditions precursors of these steroids also may escape into the circulation These secreted hormones circulate in the blood loosely bound to proteins and are degraded by the liver Complete destruction of the phenanthrene nucleus does not occur The steroids are chemically transformed to a more reduced state and are metabolized in accordance with certain general principles (Fig 80) as follows (1) The $\alpha\beta$ unsaturated carbonyl group in ring A is reduced to a saturated ketone or alcohol (2) The carbonyl group at C 20 may be unaltered or converted to a secondary α or β hydroxyl group (3) The tertiary C 17 hydroxyl group plus a vicinal oxygen at C 20 can be cleaved to a C 19 steroid and excreted as a 17 ketosteroid (4) The hydroxyl group at C 21 also may be reduced

In addition to the catabolic transformations the metabolites are conjugated as glucuronates sulfates or other forms as yet unidentified They are excreted mostly as conjugates Of the various excretory pathways available for the catabolic steroidal products in man the urinary route is by far the most important These urinary products can be analyzed and may give valuable information relative to the state of adrenocortical function

The Urinary Steroids The more abundant C 21 urinary steroids are shown in Figure 80 These are mostly catabolic products of hydrocortisone All except cortol and cortolone may be determined chemically by modifications of the Porter Silber method for 17 OH corticosteroids Since cortol and cortolone are important urinary metabolites this is a major drawback to the Porter Silber method However Norymberski has recently devised a method for determining the 17 OH corticoids which also detects cortol and cortolone The metabolites so detected are referred to as "ketogenic steroids since in the method of analysis the side chain is cleaved by oxidation to a 17 ketosteroid

The major urinary 17 ketosteroids are shown in Figure 81 Those 17 ketosteroids containing an oxygen group at C 11 are degradation products of hydrocortisone and comprise about 20 per cent of the total The secretory precursors of androsterone etiocholanolone and dehydroisoandrosterone are not completely known Androsterone and etiocholanolone do arise from the transformation of testosterone and Δ^4androstenedione but these precursors could

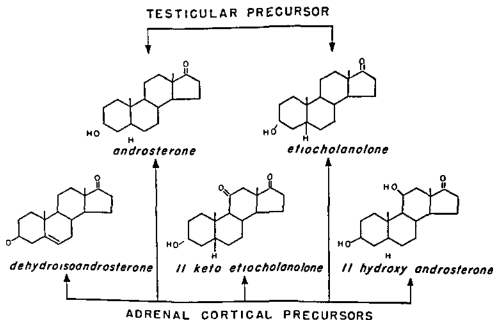


Fig 81 Precursors of the most abundant 17 ketosteroids

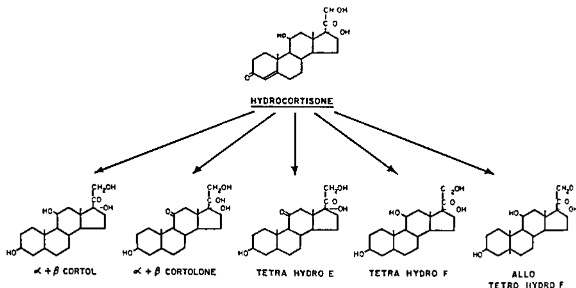


FIG 80 Major urinary 17 OH corticosteroid metabolites of hydrocortisone

tions Information is also available relative to the conditions necessary for activity of some of the enzyme systems involved

There is evidence also that acetate may act as a precursor for the adrenal steroids without intermediary formation of cholesterol This has definitely been shown to be the pathway of estrogen synthesis but a corresponding pathway for the formation of C 21 and C 19 steroids in the adrenal glands has not been conclusively demonstrated

The Control of Corticotropin Secretion Since the classic demonstration by P E Smith that the adrenal the thyroid and the gonads are dependent upon pituitary secretions chemists have attempted to isolate the tropic hormones in pure form This has been successful for the adrenocorticotropic hormone which has been shown to be a polypeptide Whereas ACTH is effective in stimulating the secretion of the glucocorticoids the secretion of aldosterone seems to be independent of pituitary control

There is a basic level of ACTH secretion by the pituitary In response to many different types of stress the pituitary secretes a greater amount of ACTH which in turn results in the increased secretion of the adrenal steroids that are necessary for homeostasis ACTH secretion is dependent upon several factors (1) *Hormonal control* The level of circulating adrenal steroid is a controlling factor of ACTH secretion In the absence of circulating steroids *e g* adrenal insufficiency increased amounts of ACTH have been detected in the circulating blood On the other hand the prolonged administration of cortisone leads to adrenal atrophy This is indicative of ACTH suppression (2) *Hypothalamic control* There are centers in the hypothalamus probably in the median eminence which also control the release and the rate of the synthesis of ACTH It has been demonstrated in the experimental animal that small destructive lesions restricted to the median eminence prevent the secretion of ACTH in response to stress In addition a protein like substance has been isolated from hypothalamic tissue which is capable of stimulating ACTH secretion by the pituitary This hypothalamic control is probably mediated by a neurohumor which is transported via the hypophysial portal system to the pituitary gland

Action of ACTH on the Adrenal Cortex The administration of ACTH causes an almost immediate fall in the concentration of both cholesterol and ascorbic acid in the adrenal cortex It has been claimed by Hechter that when ACTH is incubated with adrenal tissue there is a greater increase in the production of hydrocortisone when cholesterol is used as a substrate than if progesterone is used Consequently Hechter infers that ACTH has its effect on the biosynthetic mechanism at a point prior to the production of progesterone perhaps by cleaving off the side chain of cholesterol and facilitating the synthesis of pregnenolone In addition it is claimed that when acetate is used as a precursor the addition of ACTH to adrenal slices has no effect on the output of hydrocortisone The latter observation would indicate that the small amount of hydrocortisone which may be produced in the absence of pituitary stimu

DISEASES OF THE ADRENAL GLANDS

Introduction

The first known description of the adrenal glands is recorded in *Opuscula Anatomica Venetus* (1563) by the great anatomist of the Renaissance Bartholomaeus Eustachius Scantoseverinatus It is of interest that Eustachius described these structures as glands although their function was not at all understood Meckel s studies in 1806 deserve particular consideration because he introduced new methods of studying adrenal gland function by destroying the organ within living animals and by studying the organ in different types of animals It was not until 1855 however in Thomas Addison s classic description of a clinical syndrome which resulted from destruction of the adrenal glands that the vital function of these organs was really appreciated Shortly thereafter Brown Sequard demonstrated conclusively that complete removal of both adrenals was followed promptly by death of the experimental animal The studies of Vulpian Oliver Schaeffer Abel Takamine and Aldrich ultimately resulted in isolation of epinephrine from the adrenal medulla but since the relationship between medullary secretion and cortical secretion was not understood it was with some disappointment that epinephrine was found to be ineffective in the treatment of Addison s disease This observation however stimulated further experimental work in which it was demonstrated that the complete removal of one adrenal accompanied by the destruction of the medulla of the remaining adrenal did not give rise to the classic signs and symptoms of adrenal insufficiency From these observations it appeared that the 'life maintaining" substance liberated by the adrenal was derived from the cells of the cortex

In 1927 Hartman MacArthur and Hartman and Rogoff and Stewart independently reported the preparation of adrenal cortical extracts which were capable on injection of prolonging the survival period of adrenalectomized animals In 1930 Swingle and Pfiffner and Hartman and Brownell independently described methods of preparing adrenal cortical extracts of much greater potency

The classic studies of Loeb and Harrop demonstrated the beneficial effect of sodium salts in the treatment of patients with Addison s disease Not only was a diet of high sodium content beneficial but the studies of Truszkowski and Zwemer and Wilder demonstrated the advantages of a low potassium intake in patients with adrenal insufficiency

In 1933 both Kendall and Grollman obtained crystalline material from adrenal cortical extracts This material appeared to have cortical hormone like activity Somewhat later Reichstein isolated a crystalline compound from the adrenal cortex which had cortical hormone like activity and which he identified and named "corticosterone Subsequently Kendall demonstrated that the active compound which he had described was identical with that of Reichstein s corticosterone In 1937 Steiger and Reichstein announced the synthesis from *stigmasterol* of a steroid compound *desoxy corticosterone acetate* This compound was found to have cortical hormone like activity and was noted to be closely related chemically to progesterone The development by Reichstein Kendall and Sarret of procedures for placing an oxygen atom on the 11 and 17 carbon atoms of the steroid nucleus led to the preparation of cortisone and hydrocortisone for therapeutic use In 1952 Simpson Tait and Bush employing a chromatographic separation were able to isolate a very potent sodium retaining factor from adrenal venous blood This they termed electrocortin " The collaboration of Wettstein Neher von Euw Schneider and Reichstein with Simpson and Tait resulted in 1954 in the elucidation of the chemical structure of electrocortin as the 18 aldehyde of corticosterone It was accordingly given the name of aldosterone The synthesis of aldosterone was achieved by Schmidlin Anner Billeter and Wettstein in 1955 and its identification as the sodium retaining factor in the urine of patients with nephrosis and heart failure was subsequently established by Luetscher Neher and Wettstein

account for only a small amount of the total

The Assessment of Adrenal Function The normal values for the plasma 17 OH corticosteroids and urinary 17 ketosteroids 17 OH corticosteroids and ketogenic steroids are presented in the table of Normal Values of Clinical Importance (Appendix) The values are usually depressed in both primary and secondary adrenal insufficiency but there may be an overlap with levels obtained in endocrinologically normal persons Decreased concentrations of urinary steroids to the administration of the chronic diseases The finding of low levels of urinary steroids in itself is not diagnostic of adrenal insufficiency However the response of both the plasma and urinary steroids to the administration of exogenous corticotropin may be of great value in assessing adrenal function since the administration of ACTH results in no increase in these values in the absence of functioning adrenals

The corticosteroids are usually elevated in Cushing s syndrome whereas there may be little or no increase in the urinary 17 ketosteroids in this condition On the other hand the various virilizing syndromes are characterized by the finding of elevated 17 ketosteroids and normal or even low 17-OH corticosteroids

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followed complete relief of the associated hypertension

Pheochromocytomas are comparatively rare In 1950 Smithwick collected 270 cases from the literature (67 per cent dem strated only at autopsy) A recent apparent increase in the incidence of these tumors may be accounted for by the use of new diagnostic agents by careful search among hypertensive patients for curable forms of hypertension and by the increased oppor tunity to detect chromaffin tumors when operations are being performed on the thoracolumbar sympathetic chain for the treatment of hypertension

Pheochromocytomas occur in all age groups but are more frequent in adults There is no sex predilection

Pathology In 10 to 20 per cent of cases the tumors are multiple In a similar num ber of instances the tumors have been found outside the adrenal in chromaffin tissue in the paraganglia along the retro pleural and retroperitoneal chains of the sympathetic nervous system in the carotid bodies or the organs of Zuckerkandl An associated neurofibromatosis has been ob served in 5 per cent of cases Approximately 10 per cent of the tumors are malignant and metastasize to regional and thoracic lymph nodes liver and skeleton

The tumors vary in size but are fre quently quite small They are usually lobu lated highly vascular and well encapsu lated The cut surface is yellowish brown in color and frequently shows evidence of hemorrhage and cystic degeneration Micro scopically the tumor cells are large irregu lar or polyhedral in shape and have a gran ular cytoplasm

Clinical Picture The manifestations of pheochromocytoma are the result of an in creased secretion of norepinephrine and epinephrine Two distinct syndromes oc cur one associated with intermittent or paroxysmal hypertension and the other characterized by persistent hypertension

In 35 to 50 per cent of cases classic paroxysms adrenosympathetic crises " oc cur These may be precipitated by such events as emotional upsets physical exer tion or changes in posture Early the at tacks tend to occur at long intervals and last only a few minutes Later they may be more frequent and severe lasting many hours The attacks are characterized by severe anxiety throbbing headache force ful palpitation tremulousness visual blur ring nausea sometimes vomiting oc casionally retrosternal chest pain and a rise in blood pressure which may attain a systolic level of 300 mm of mercury or more The diastolic blood pressure may rise to a level of 175 mm of mercury The extremities are cold and often pale the neck veins distended the pupils dilated and the skin soaked with perspiration Hy perglycemia and glycosuria during attacks are common Prolonged episodes may ter minate in a shock like state with hyper pyrexia and hypotension Death may occur from pulmonary edema ventricular fibril lation or cerebral hemorrhage

In many cases of pheochromocytoma there is sustained hypertension The course of the disease is not unlike that of essential hypertension with progressive cardiovas cular renal and retinal involvement The basal metabolic rate is often elevated and frank diabetes may be encountered Chemi cal analysis of tumors in these cases usually reveals a marked preponderance of nor epinephrine

Diagnosis This may be established by the history of a typical attack or by deliberately precipitating an attack through change in position or direct pressure upon the tumor In a small percentage of cases a tumor or a displaced kidney may be palpated in the flank Pyelography may reveal depression of the renal shadow Perirenal and more re cently presacral insufflation of oxygen have been employed to outline a tumor mass

Certain pharmacological tests may be of considerable aid in the diagnosis of pheo chromocytoma Two types of test are used In one the provocative test a paroxysm of hypertension is precipitated when the blood pressure has been normal In the other the blocking test a fall in blood pressure is induced by the use of an adrenolytic com pound when the pressure has been elevated Of the provocative agents histamine prob-ably provides the most reliable response but both false negative and false positive responses have been reported *Histamine phosphate* when given intravenously in a dose of 0 01 to 0 025 mg induces a flush headache and a slight blood pressure fall in the normal subject A rise in blood pressure significantly greater than the cold pressor response within two minutes of injection is considered a positive test This occurs in many but by no means all cases of pheo-chromocytoma Sometimes alarming rises in blood pressure occur which may be dan gerous in patients with advanced arterial disease In these instances Regitine 5 mg should be administered intravenously

Diseases of the Adrenal Medulla

The cells of the adrenal medulla are of ectodermal origin and arise as do the cells of the sympathetic nervous system from the primitive neural crest The parent cell is the sympathogone This cell may differentiate to form a sympathoblast or neuroblast and finally a mature ganglion cell or it may give rise to a chromaffin cell The latter is so named because of the brown color which the granules of its cytoplasm assume when treated with chromic acid salts

These cell types are found not only in the adrenal medulla but wherever sympathetic nervous tissue occurs particularly in the ganglia and in the organs of Zuckerkandl at the bifurcation of the aorta Tumors may develop from any of these cell types

Hormones of the Adrenal Medulla Epinephrine was the first hormone to be isolated (Abel 1897) and chemically identified (Aldrich 1901) In 1949 von Euler isolated norepinephrine from the adrenal medulla and from adrenergic nerve fibers thereby establishing the existence of two medullary hormones Structurally these two hormones are catecholamines and differ only in the fact that norepinephrine lacks the N methyl group possessed by epinephrine (Fig 82) The epinephrine and norepinephrine content of human adrenal medullary tissue has been estimated biologically by von Euler to be 2 4 to 4 0 mg per gm of which 10 to 30 per cent is norepinephrine The total plasma concentration of epinephrine and norepinephrine is approximately 3 micrograms per liter norepinephrine makes up approximately 80 per cent of this value The urine normally contains between 15 and 45 micrograms of catecholamines per day 85 per cent of this is norepinephrine The preponderance of norepinephrine in both plasma and urine in the face of a low norepinephrine epinephrine ratio in the adrenal medulla is thought to reflect the liberation of additional quantities of this humoral agent from adrenergic nerve endings In contrast to normal medullary tissue in which the predominant hormone is epinephrine actively secreting adrenal medullary tumors pheochromocytomas often contain large amounts of norepinephrine

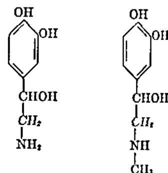


FIG 82 Adrenal medullary hormones

Pharmacological studies have shown important differences in the actions of epinephrine and norepinephrine Both hormones raise the blood pressure but by different mechanisms Epinephrine causes an increased cardiac output and with the exception of the skin vessels generalized vasodilatation The cardiac rate increases the systolic pressure rises but the diastolic pressure shows little change Norepinephrine on the other hand causes marked peripheral vasoconstriction with a rise in both systolic and diastolic blood pressure The cardiac output is little altered and the heart rate may be slowed Epinephrine has a prominent metabolic effect which is possessed to only a very limited extent by norepinephrine It causes increased oxygen consumption with a rise in body temperature and basal metabolic rate Furthermore it accelerates hepatic glycogenolysis with a consequent rise in fasting blood sugar levels and often a diabetic type of glucose tolerance curve Muscle glycogen is broken down more rapidly to lactic acid Epinephrine causes a significant fall in the level of circulating eosinophils but actual stimulation of the adrenal cortex has not been demonstrated to occur in man

Despite the important physiological effects of the adrenal medullary hormones the adrenal medulla is apparently not essential for life It is however a valuable adjunct to the adrenal cortex in aiding the organism to cope with acute stress Instances of adrenal medullary insufficiency have not been recognized clinically

ADRENAL MEDULLARY HYPERFUNCTION

(Pheochromocytoma)

Pheochromocytomas are actively secreting tumors arising in the chromaffin tissue of the adrenal medulla or the paraganglia of the sympathetic nervous system The first description of the association of paroxysmal hypertension and pheochromocytoma was given by Labbe in 1922 In 1927 C H Mayo removed such a tumor and there

It contains many mature ganglion cells separated by a network of myelinated or nonmyelinated nerve fibers

Neuroblastoma (*Sympathoblastoma*) This highly malignant tumor occurs almost exclusively in infancy and early childhood Except for renal embryoma (Wilms tumor) neuroblastoma is the commonest retroperitoneal malignant tumor of children In approximately 50 per cent of cases these tumors are extra adrenal arising retroperitoneally or retropleurally in the sympathetic chain the celiac ganglia the organs of Zuckerkandl the cerviosympathetic ganglia or from the substance of the central nervous system The tumor metastasizes early to regional lymph nodes liver bones and orbit

Pathologically the tumors are large and cellular The cut surface is firm with many areas of hemorrhage and necrosis The cells which are oval with dark brown nuclei and thin rims of cytoplasm are often arranged in rosette fashion and separated by fine fibrils

The manifestations of a neuroblastoma may be those of a local tumor mass with abdominal enlargement vomiting and pain or they may be those of a generalized malignancy with weakness loss of weight fever and anemia In one quarter of the cases there is generalized lymphadenopathy In some instances metastases may introduce the disease and the child may present swellings in the skull proptosis and ecchymoses of the eyelids

Radical surgery followed by deep x ray therapy is the treatment of choice Although the prognosis is poor Farber reported 10 cures in 40 cases treated in the above manner and followed over a ten year period In some of these children complete surgical removal of the tumor had not been possible

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Diseases of the Adrenal Cortex

INTRODUCTION

During the past two decades approximately thirty steroid compounds have been isolated from the adrenal cortex Six of these which are capable of maintaining life in adrenalectomized animals have been identified hydrocortisone (Compound F) cortisone (Compound E) corticosterone (Compound D) dehydrocorticosterone (Compound A) desoxycorticosterone (DOC) and the recently isolated aldosterone Those compounds which possess an alpha ketol side chain (CO-CH OH) at carbon 17 are termed "corticoids" Compounds A B E and F and aldosterone which possess an oxygen atom at a carbon 11 are "11-oxygenated corticoids" Compounds E and F are "11 17-oxygenated corticoids"

Hydrocortisone (Compound F) and cortisone (Compound E) exhibit most of the known effects of the adrenal cortex when administered to adrenalectomized human subjects While these compounds have a relatively weak electrolyte regulating activity when given by mouth or by intramuscular injection they are capable of producing a profound sodium retention when administered continuously by the intravenous route Desoxycorticosterone while strongly sodium retaining has little effect on intermediary protein fat and carbohydrate metabolism Aldosterone which is a derivative of corticosterone with an aldehyde group at carbon 18 is twenty to thirty times as active in sodium retention as desoxycorticosterone and appears to be more effective than desoxycorticosterone in its influence on carbohydrate metabolism Corticosterone (Compound B) and dehydrocorticosterone (Compound A) stand halfway between hydrocortisone and desoxycorticosterone in terms of the physiological activities which they exhibit Unlike hydrocortisone and cortisone they do not induce an eosinopenia or lymphopenia Although many steroids have been isolated from adrenal cortical tissue it would appear from studies on adrenal venous blood that the human adrenal cortex secretes mainly hydrocortisone corticosterone aldosterone and an androgenic 17 ketosteroid androstenedione of these hydrocortisone is secreted in the greatest amount Desoxycorticosterone does not appear to be a natural secretory product of the adrenal cortex Catabolism of the adrenal steroids

Methacholine hydrochloride (Mecholyl) when given subcutaneously in doses of 12 5 to 25 mg to a normal subject produces salivation sweating and a transient fall followed by a mild rise in blood pressure A striking rise in blood pressure may occur when pheochromocytoma is present but as with the histamine test both false negative and false positive tests occur Alarming reactions may be seen and the subcutaneous administration of 1 0 mg of atropine sulfate prior to the injection of the Mecholyl is recommended

Of the blocking agents Benzodioxane and Regitine are the most reliable *Benzodioxane* (*piperoxanhydrochloride*) is structurally related to epinephrine It exerts an antipressor effect while retaining certain sympathomimetic actions When given intravenously over a two minute period in a dose of 10 mg per square meter of body surface it causes agitation tachycardia flush headache and dizziness In the normal subject there is a slight rise in blood pressure When a pheochromocytoma is present the pressure usually falls at least 35 mm of mercury False positive tests are extremely uncommon although false negatives occur not infrequently *Regitine* (*phentolamine*) has a similar antipressor action without unpleasant side effects When given intravenously in a 5 mg dose a similar blood pressure fall occurs if a pheochromocytoma is present

In the performance of these tests it is important to have the patient resting quietly to establish a good baseline blood pressure When sedatives have been administered within twenty four hours of the test false reactions may occur The responses in uremic patients are unreliable

In 1950 Engel and von Euler observed a marked increase in the urinary excretion of catecholamines in the presence of pheochromocytoma This finding has been confirmed by Goldenberg employing a fluorometric technique rather than a biological assay Recently the histamine test has been combined with blood catechol amine analysis Elevated levels of catechol amines may be observed two to ten minutes after the administration of 0 025 mg of histamine posphate given intravenously Normal subjects and hypertensive patients without pheochromocytoma do not show this reaction

Treatment Surgical excision of the tumor may result in complete remission of symptoms although in certain instances in which the hypertension has been persistent and of long duration little change in blood pressure may occur following operation The transperitoneal approach allows satisfactory exploration of all possible tumor sites in the abdomen Two serious events may occur during operation (1) The blood pressure may rise to extreme heights or fatal cardiac arrhythmias may occur due to excessive discharge of medullary hormones or (2) following resection of the tumor the blood pressure may fall precipitously and profound shock ensue due to abrupt withdrawal of circulating hormones Adequate preoperative sedation is important Anesthetic agents likely to produce serious cardiac arrhythmias in the presence of high epinephrine levels—cyclopropane ethyl chloride—should not be employed Induction with Pentothal followed by intratracheal nitrous oxide—ether with high oxygen saturation provides satisfactory anesthesia Ligation of the blood supply of the tumor before handling will reduce the likelihood of precipitating a hypertensive episode The latter can be corrected by the use of intravenous Regitine which should be kept ready during the operation and administered when indicated The precipitous fall in blood pressure which often occurs following ligation of the tumor vessels can be managed by the use of intravenous norepinephrine During the postoperative period Neo Synephrine may be given subcutaneously to correct mild hypotensive episodes Once the immediate postoperative period is over patients usually do well and symptoms and hypertension disappear

Because of the excellent results of surgical treatment it is of the utmost importance to consider the possibility of pheochromocytoma in all hypertensive patients

NONFUNCTIONING TUMORS ARISING FROM MEDULLARY TISSUE

These tumors may arise from any of the primitive or mature cells of the sympathetic nervous system and the adrenal medulla

The *sympathogonioma* is a rare highly malignant tumor which appears in early infancy or intrauterine life It is a large soft cellular growth which often shows evidence of hemorrhage and necrosis It metastasizes early to retroperitoneal lymph nodes liver and bone The prognosis is poor

The *ganglioneuroma* on the other hand is a small well encapsulated slow growing tumor which occurs in adults and is usually an incidental finding at post mortem

fluids It can also be obtained as the acetate in crystalline suspension in saline solution (25 mg per ml) and in the form of scored tablets (20 10 and 5 mg)

2 **Cortisone** This hormone is available as the acetate (a) as a crystalline suspension in saline solution which is suitable for intramuscular injection and of which 1 0 ml contains 25 mg of hormone and (b) as scored tablets 5 and 25 mg for oral use

3 **Prednisone and Prednisolone** These substances are four to five times as potent as cortisone and hydrocortisone and have much less sodium retaining activity They are available in 5 mg tablets

4 **Nine alpha fluorohydrocortisone** This substance is approximately 25 times as potent as cortisone and hydrocortisone in carbohydrate activity and exhibits marked salt retaining activity as well It is available in tablets of 1 0 and 0 1 mg

5 **Desoxycorticosterone** This hormone is available in three forms (a) as the acetate dissolved in sesame oil for intramuscular injection 5 mg of the hormone in 1 0 ml (b) as the acetate in the form of tablets known as linguets or buccalets containing 2 or 5 mg of the hormone in inert vehicles for direct sublingual absorption (c) synthetic desoxycorticosterone trimethylacetate a crystalline suspension of slowly hydrolyzed microcrystals acting for approximately four weeks after intramuscular injection 25 mg once a month being equivalent to 1 mg daily of desoxycorticosterone acetate in oil

6 **Corticotropin** Corticotropin (ACTH) is available as (a) lyophilized powder 10 to 40 U S P units per vial which can be administered in aqueous solution either intravenously or by intramuscular injection by which route it has a duration of action of six to eight hours or (b) as a long acting gel preparation (duration of action eighteen to twenty four hours) 20 to 80 U S P units per ml Gel preparations must be kept refrigerated and must be warmed to 50 C before being taken up in a syringe Since ACTH is a polypeptide sensitivity reactions may be encountered particularly in patients with primary adrenal insufficiency who have not received cortisone

HYPOFUNCTION OF THE ADRENAL CORTEX

The various types of adrenal insufficiency may be classified as follows

1 Acute adrenal cortical insufficiency
   (a) Adrenal crisis (in patients with Addison s disease)
   (b) Adrenal hemorrhage
   (c) Surgical (following adrenalectomy or resection of hyperfunctioning adrenal tissue)
   (d) Iatrogenic—induced by ACTH cortisone or hydrocortisone therapy
2 Chronic adrenal cortical insufficiency
   (a) Primary (Addison s disease)
   (b) Secondary (hypopituitarism)
   (c) Surgical (following adrenalectomy)
   (d) Insufficiency associated with androgenic adrenal hyperplasia

ACUTE ADRENAL CORTICAL INSUFFICIENCY

Adrenal Crisis An adrenal crisis represents a severe acute exacerbation of Addison s disease Although present-day substitution therapy has materially reduced the frequency of adrenal crisis the advent of infection trauma or gastrointestinal upsets in patients with Addison s disease unless combated by an immediate increase in hormone dosage may rapidly lead to the development of acute adrenal insufficiency The classic manifestations of adrenal crisis are anorexia nausea vomiting headache diarrhea abdominal pain dehydration hypotension restlessness marked weakness and lethargy Hyperpyrexia, often extreme usually occurs but subnormal temperatures may be encountered even in the presence of infection Ultimately coma and vascular collapse ensue It should be emphasized however that in well treated patients especially those who have received desoxycorticosterone hypotension and shock may only occur terminally Laboratory study usually but not invariably reveals hyponatremia hyperkalemia hypoglycemia and azotemia

The necessity for immediate and vigorous treatment of adrenal crisis is strongly emphasized Therapy is directed at the provision of adequate adrenal cortical hormone the control of infection and support of the cardiovascular system

1 A continuous intravenous infusion of 5 per cent glucose in normal saline is started immediately Hydrocortisone (200 mg) is administered in 5 per cent glucose by a separate intravenous infusion If an intravenous preparation of hydrocortisone is not available cortisone acetate is given intramuscularly in an initial total dose of 200 mg (in four different sites) Thereafter the hormone may be given orally and the dosage gradually tapered to a maintenance level of 25 mg per day

and the role of the pituitary gland in their elaboration and secretion are discussed in the section on Steroid Metabolism

Functions of the Adrenal Cortex The *functions of the adrenal cortex as medi ated by the adrenal cortical steroids are as follows*

Regulation of Sodium Potassium and Chloride Metabolism The 11 oxygenated corticoids increase the reabsorption of sodi um and chloride by the renal tubules and decrease the sodium chloride loss in sweat salivary gland and gastrointestinal secre tion The administration of these com pounds results in an initial and inconstant *rise of urinary potassium excretion* There may follow a brief period of potassium re tention probably associated with the depo sition of glycogen in the liver Thereafter one observes a continued loss of potassium This is induced by the antianabolic action of these steroids which leads to liberation of nitrogen potassium and phosphate from intracellular sources Whereas all of the foregoing electrolyte changes may be observed following large doses of the 11 *oxygenated corticoids only part of the pat* tern is exhibited by desoxycorticosterone which has no oxygen atom at carbon 11 and which lacks an antianabolic action and an effect on glycogen synthesis Removal of the adrenals is followed by sodium chlo ride and water loss potassium retention dehydration and circulatory collapse

Regulation of Water Balance Water re tention is observed following corticoid ad ministration This appears to be largely a reflection of sodium retention Aldosterone favors an increase in extracellular sodium chloride and water The 11 17 oxygenated corticoids hydrocortisone and cortisone appear to exert a regulatory effect on in tracellular water facilitating water loss from cells in the presence of excessive cel lular hydration and increasing the water *content of dehydrated cells Although the* mechanism of interaction is not known it is generally accepted that the 11 17 oxy genated corticoids antagonize the physio logical effects of the posterior pituitary anti diuretic hormone

Regulation of the Metabolism of Carbo hydrate Protein and Fat The 11 oxy genated corticoids particularly hydrocorti sone and cortisone have an anti insulin effect An antianabolic effect leads to in creased gluconeogenesis from protein The role of the 11-oxygenated corticoids in fat metabolism is not clear It would appear that there is increased mobilization and utilization of fat which is not accompanied by appreciable ketosis *The net over all effect* of these adrenal steroids is increased gluco neogenesis from protein and possibly fat

Androgenic Function The development of axillary hair in the male and female and of pubic hair in the female is dependent on the presence of the adrenal cortex The adrenal androgens also possess a protein anabolic effect This effect is most dramat ically seen in the rapid growth rate of the prepubertal child with the adrenogenital syndrome

Regulation of Hematopoiesis and Tissue Reactivity Only the 11 17 oxygenated corti coids hydrocortisone and cortisone exert significant hematological effects These consist of an eosinopenia in all probability due to increased peripheral destruction a lymphopenia due to increased lysis of both fixed and circulating lymphocytes a neu triphilia and a tendency to polycythemia With large doses of hydrocortisone or corti sone the reactivity of mesenchymal tissues to injury irritants and foreign proteins (including microorganisms) may be greatly inhibited As a result of this inhibi *tory effect on both fixed and mobile cellular* defenses inflammation is reduced but re sistance to injury and infection may be seriously impaired

Control of Pigmentation Primary ad renal cortical insufficiency is accompanied by an increased deposition of melanin in the skin Following bilateral adrenalectomy this may be inhibited by the daily adminis tration of hydrocortisone or cortisone Des oxycorticosterone is ineffective in this regard The absence of pigmentation in most cases of secondary adrenal insuffi ciency indicates that an intact anterior pituitary is necessary for this phenomenon to occur There is evidence to suggest that in the absence of the adrenal cortex there is an increased secretion of a melanophore stimulating substance from the anterior *pituitary gland*

Effects on the Gastrointestinal Tract Hy drocortisone and cortisone increase the secretion of hydrochloric acid and pepsin by the stomach and of the pancreatic en zymes as well These steroids also appear to facilitate the absorption of fat from the intestinal tract

ADRENOCORTICAL HORMONE AND CORTI COTROPIN PREPARATIONS AVAILABLE FOR CLINICAL USE

1 Hydrocortisone *This hormone is avail* able as the free alcohol in ampules con taining 100 mg in 20 ml of 50 per cent ethyl alcohol for addition to intravenous

surgical operation is imposed the adrenal cortex may not respond adequately enough and a state of relative adrenal insufficiency may ensue This may occur during the period of ACTH or cortisone administration or following the discontinuance of hormone therapy before the responsiveness of the pituitary adrenal cortical axis has returned to normal An adrenal crisis which may arise under these circumstances must be anticipated and supplementary hydrocortisone or cortisone administered until the period of stress has ended

CHRONIC ADRENAL CORTICAL INSUFFICIENCY

PRIMARY FAILURE (ADDISON S DISEASE)

Incidence and Etiology True Addison s disease is a relatively rare condition the incidence approximating one case per 100 000 population There are two major causes of this condition fibrocaseous tuberculosis of the adrenal gland and an idiopathic process leading to bilateral adrenal cortical atrophy In earlier reports the incidence of tuberculosis of the adrenal glands as a cause of Addison s disease was as high as 80 to 90 per cent More recently the incidence of tuberculosis has diminished and approximately 50 per cent of cases are nontuberculous in origin In a small percentage of patients other lesions may be encountered such as bilateral tumor metastases leukemic infiltration amyloidosis hemochromatosis and histoplasmosis

Clinical Picture The onset of the disease is usually insidious Occasionally however the first evidence of adrenal failure may be the development of crisis precipitated by an acute infection or a surgical operation The predominant symptoms are asthenia easy fatigability weight loss increased pigmentation of the skin and mucous membranes gastrointestinal complaints including anorexia nausea vomiting diarrhea and abdominal pain and episodes suggestive of hypoglycemia Increased irritability nervousness emotional instability and periods of depression and negativism are not uncommon Pigmentation usually appears early and is the most striking physical evidence of the disease It usually presents itself as a diffuse tanning with increased pigmentation over pressure points such as the knees elbows and knuckles There may be bluish black pigmentation of the mucous membranes and multiple black freckles over the body Not infrequently vitiliginous areas or "leukoderma may be noted Most patients with Addison s disease have hypotension and a small heart Secondary sex characteristics are usually little affected except for the reduction of the growth of axillary and body hair The menstrual cycle and gonadal function are ordinarily remarkably well maintained

Laboratory Findings There is a normochromic normocytic anemia which be

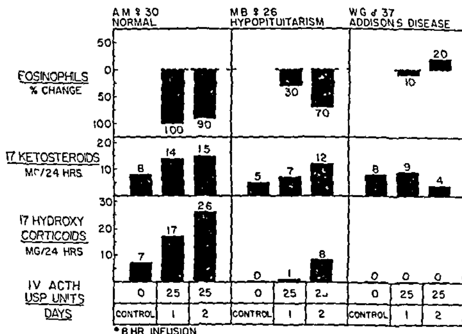


Fig 83 Adrenal responses to intravenous ACTH

2 Penicillin is given by intramuscular injection in a minimal dosage of 400 000 units every six hours

3 If shock is profound or if hypotension persists Neo Synephrine may be injected subcutaneously in a dose of 0 3 to 0 5 mg every one to two hours or 5 to 10 mg may be added to the intravenous infusion and the rate adjusted to maintain blood pressure at normal levels Infusions of norepinephrine may also be employed to maintain the blood pressure In the presence of extreme persistent shock it may be necessary to administer a transfusion of whole blood or concentrated serum albumin Since the sodium retaining effect of *intravenously* administered hydrocortisone is marked it is usually not necessary to give desoxycorticosterone during the acute phase of adrenal crisis unless the hypotension is refractory to other measures In the latter situation 10 to 20 mg of the hormone may be injected intramuscularly initially and 2 5 to 5 0 mg per day thereafter

Adrenal Hemorrhage The causes and manifestations of massive bilateral adrenal hemorrhage vary with age In the newborn infant adrenal hemorrhage may occur during a prolonged and difficult labor especially when asphyxia and traumatic resuscitation procedures are involved In older children and adults adrenal apoplexy is usually associated with overwhelming sepsis (Waterhouse Friderichsen syndrome) Meningococcus has been the causative organism in approximately 75 per cent of cases other organisms have been the staphylococcus streptococcus and pneumococcus In a few adult cases adrenal hemorrhage has occurred as a result of anticoagulant overdosage

Pathologically there is extensive bilateral adrenal hemorrhage which may occasionally rupture through the capsule of the adrenal into the peritoneal cavity In those cases associated with a fulminating sepsis a widespread capillary and arteriolar necrosis is frequently observed Frank meningitis is rarely seen

Acute adrenal insufficiency at birth produces the characteristic picture of acute shock hemorrhagic manifestations are usually absent although in some cases a retroperitoneal mass may be palpated Later in life when the disease is associated with an overwhelming septicemia there are extensive cutaneous petechiae and purpura Early symptoms in these cases are increased irritability nausea vomiting abdominal pain and headache Shortly after the onset of the disease a petechial rash appears which progresses to form a diffuse confluent purpuric eruption Fever is present early and the temperature may rise to extreme levels Intense cyanosis develops and finally circulatory collapse ensues Death usually occurs within twenty four to forty eight hours after the onset of symptoms As blood cultures are not always positive specific therapy should not await the report of bacterial growth In some cases the meningococcus can be seen on a Gram stain of fluid obtained from carefully punctured petechial spots

The specific diagnosis of adrenal insufficiency under these circumstances is difficult to establish Blood steroid analysis provides the most reliable method in the acute case Since the emergency is critical blood should be withdrawn for hormone determination and treatment for adrenal crisis instituted empirically until the results of the chemical analysis are known Eosinopenia favors but does not prove acute adrenal insufficiency

Treatment is similar to that outlined under Adrenal Crisis Control of the infection is of course absolutely essential Although formerly the Waterhouse Friderichsen syndrome uniformly fatal in recent years several instances of recovery have been reported It should be emphasized however that meningococcemia with purpuric rash may be associated with circulatory collapse in the absence of adrenal hemorrhage and without pathological evidence of acute adrenal cortical insufficiency

Acute Adrenal Insufficiency Associated with Surgery of the Adrenal Gland This condition may occur following bilateral adrenalectomy or the removal of a unilateral adrenal cortical tumor which is associated with atrophy of the contralateral gland Adrenal insufficiency should of course be anticipated under these conditions and adrenal cortical hormone replacement therapy instituted during and after operation as described in the section on the Treatment of Cushing s Syndrome (see table p 740)

Acute Adrenal Insufficiency Associated with ACTH or Cortisone Therapy The commonest cause of acute adrenal cortical insufficiency is that which occurs in association with prolonged ACTH or cortisone administration Here there is a diminished reactivity of the pituitary adrenal cortical system due to pituitary inhibition in the case of ACTH administration and to both pituitary and adrenal cortical inhibition in the cases of cortisone treatment When the stress of a severe medical illness or a

per day Each of these hormones is best given in divided doses at 8 A M and 3 P M Similar doses of cortisone and hydrocortisone when given daily to patients with Addison's disease and active tuberculosis do not appear to promote the spread of the infectious process

During periods of intercurrent illness it is essential that the dose of cortisone be increased to a level of 75 to 100 mg per day If the administration of the hormone by the oral route is not possible the aqueous suspension of cortisone acetate may be given intramuscularly in equivalent doses Patients with Addison's disease who undergo surgery should be adequately prepared with supplementary hormone It is recommended that for major surgery in Addisonian patients a therapeutic program similar to that described for patients undergoing adrenal surgery for Cushing's syndrome should be instituted (see table p 740)

Unfortunately the amounts of cortisone or hydrocortisone required to restore to normal the metabolism of carbohydrate protein and fat are too small to assure normal electrolyte and water balance Thus adequate hydration and blood pressure stabilization require either the use of 10 to 15 gm of supplementary sodium chloride per day or in the vast majority of cases the use of small amounts of desoxycorticosterone acetate (DCA) with a normal sodium and potassium intake It is customary to give 2 5 to 5 0 mg of desoxycortisone acetate in oil once daily intramuscularly or 25 to 75 mg of long acting trimethylacetate ester intramuscularly once monthly or 0 1 to 0 5 mg of fluorohydrocortisone once daily by mouth Body weight blood pressure heart size and serum potassium are followed the dose being adjusted to bring these measurements within normal limits In elderly patients or in the presence of hypertension edema or cardiac enlargement all salt retaining steroid hormone therapy should be discontinued and the patient's mineral requirement should be regulated by diet alone

Because of the relatively small doses of cortisone employed in maintenance therapy undesirable effects such as are encountered in the treatment of collagen diseases are rarely seen Gastric irritation occasionally occurs in patients taking cortisone acetate by mouth This is overcome in most instances by giving the hormone during meals Increased excitability and sleeplessness are only rarely encountered if the last dose of cortisone is given no later than 4 P M Psychotic reactions are quite uncommon but occasionally occur even at low dosages This demands reduction in dosage until the patient's psyche becomes stable In view of this side effect it is advisable to start therapy with a small dose (12 5 mg per day) of the hormone

Patients with Addison's disease and those who have undergone bilateral adrenalectomy should carry a card with them at all times bearing the doctor's name telephone number and address the patient's disease his name and address and that of the nearest of kin In addition the following sentence should be written In the event of illness administer 25 mg of cortisone acetate every six hours by mouth unless the patient is unconscious when 200 mg of the hormone should be given by intramuscular injection

Prognosis In the absence of active tuberculosis the outlook is good with modern substitution therapy On DCA alone five year survival in a large group of patients was increased from 20 per cent in the salt treatment era to 50 per cent Further improvement is to be anticipated now that cortisone and hydrocortisone are available

CHRONIC ADRENAL CORTICAL INSUFFICIENCY SECONDARY TO PITUITARY FAILURE

This condition is due to an anterior pituitary insufficiency of ACTH It differs from primary adrenal insufficiency (Addison's disease) in that the electrolyte disturbance is usually less marked the susceptibility to hypoglycemia is greater and pigmentation is minimal or absent Associated deficiencies of gonadal and thyroid function are ordinarily present and in many patients dominate the clinical picture The response to ACTH is typically delayed in proportion to the degree of secondary adrenal cortical atrophy (Fig 83) Treatment involves the use of cortisone or hydrocortisone as described above for Addison's disease Desoxycorticosterone is administered if there is a significant tendency towards salt loss In addition thyroid extract and testosterone are employed as indicated

CHRONIC ADRENAL CORTICAL INSUFFICIENCY SECONDARY TO ADRENALECTOMY

Patients who have undergone total and in many instances subtotal adrenalectomy require adrenal cortical hormone replacement therapy similar to that described for Addison's disease These patients however are particularly susceptible to the effects of cortisone deprivation Moreover they may tolerate larger quantities of cortisone than

comes accentuated when rehydration is achieved There is a tendency to lymphocytosis and moderate eosinophilia In severe deficiency low serum sodium and chloride and a high serum potassium are observed Hypoglycemia may occur during extended fasting or following high carbohydrate loads Urinary 17 ketosteroid excretion is diminished in the male and may be virtually absent in the female The level of urinary 17 hydroxycorticoids is generally below 2 mg per day Although 20 to 25 per cent of patients reveal adrenal calcification on roentgenographic examination this finding is not pathognomonic of adrenal insufficiency The basal metabolic rate is often between minus 10 and minus 20 per cent The blood plasma volume is reduced The electrocardiogram characteristically shows a low voltage and there is a decreased frequency of the waves on the electroencephalogram

Diagnosis The most definitive diagnostic procedure is the demonstration of a lack of adrenal cortical response to the administration of pituitary corticotrophin (ACTH) In the 8 hour intravenous ACTH test 25 U S P units of the hormone are infused intravenously in 500 ml of 5 per cent dextrose in saline over an 8 hour period on each of three successive days Determinations of urinary 17 ketosteroids and 17 hydroxycorticoids are carried out on twenty four hour collections on a control day and on each of the three days during ACTH administration Blood is taken for an eosinophil count at the beginning and end of each infusion Under these circumstances a normal subject will exhibit an increase of 8 to 16 mg per day in the excretion of 17 hydroxycorticoids and 4 to 8 mg per day in the excretion of 17 ketosteroids while patients with Addison s disease will show virtually no response Normal subjects will respond with an eosinopenia of 80 to 90 per cent whereas Addisonian patients show little or no change Patients with hypopituitarism and ACTH insufficiency exhibit varying responses depending upon the degree of adrenal cortical involution

An alternative method of testing adrenal cortical response consists in the intramuscular injection of 40 units of ACTH gel twice daily over a two day period Urinary 17 ketosteroids and 17 hydroxycorticoids are determined on a control day and on each of the days of ACTH administration Eosinophil counts are checked before each morning injection Results are similar to those obtained with the intravenous ACTH test Occasionally a false negative response is observed when extravascular inactivation of ACTH prevents the hormone from reaching the adrenal cortex Thus with a negative response to the injection of ACTH gel one should always resort to intravenous administration of the hormone

The four hour ACTH test may be of value as a rapid screening procedure In this test the level of circulating eosinophils is determined before and four hours after the intramuscular injection of 25 U S P units of ACTH in aqueous solution A fall in circulating eosinophils exceeding 50 per cent of the initial value makes adrenal insufficiency highly unlikely A fall of less than 50 per cent may be due to adrenal cortical insufficiency but can also be caused by inadequate adrenal stimulation due to extravascular destruction of ACTH In the latter event the more definitive ACTH tests described above must be employed

The ACTH test may also be used in conjunction with blood steroid response changes in blood steroid level being observed at the beginning and end of four or eight hour infusion of 25 units of ACTH This method has not been as widely used as the twenty four hour urinary measurement but is useful in those situations in which accurate urine collections cannot be made

There is no justification today for the use of the nonspecific diagnostic tests such as water excretion salt deprivation and insulin and glucose tolerances if hormonal analyses following ACTH administration can be obtained

Treatment As a result of the remarkable advances in recent years in the preparation of crystalline adrenal steroids highly effective replacement therapy is now possible for patients with Addison s disease The prognosis of such patients has been particularly improved since the advent of cortisone The administration of this hormone leads to a restoration of appetite muscular strength and body weight and a general feeling of well being The anemia is corrected the tendency to hypoglycemia is reduced the electrocardiogram and electroencephalogram return toward normal the capacity to excrete an ingested water load improves pigmentation is lightened and the capacity to withstand the stress of intercurrent infection and trauma is greatly enhanced Adequate maintenance therapy is provided by an average daily dose of cortisone of 25 to 37 5 mg by mouth Alternatively hydrocortisone may be administered in a dose of 20 to 30 mg by mouth

ceived long term cortisone therapy In the presence of bilateral hyperplasia basophil adenoma is frequently found These tumors are small and enlargement of the sella turcica is exceedingly rare

The most striking generalized pathological change in Cushing's syndrome is protein depletion There is osteoporosis and general muscle wasting The blood vessels are fragile and frequently show changes secondary to hypertension Widespread fatty degeneration is common The kidneys reveal nephrosclerosis and calcinosis The pancreas may show fatty necrosis and islet cell hyperplasia

Clinical Picture The clinical picture of Cushing's syndrome is essentially the expression of an excessive secretion of hydrocortisone like hormones (Fig 84) The most striking feature is protein depletion which is evident in muscle skin blood vessels and bone Marked weakness is associated with diminution of muscle mass Fragility of the skin and blood vessels is evidence by depressed purple striae over the abdomen thighs and upper arms and increased susceptibility to bruises and ecchymoses Osteoporosis leads to backache and dorsal kyphosis and compression fractures of the vertebrae are not uncommon

Increased gluconeogenesis from protein and possibly fat leads to a diminished carbohydrate tolerance and occasionally diabetes

There is a striking redistribution of fat with the obesity confined to the face neck and trunk The combination of supraclavicular fat pads combined with dorsal kyphosis give rise to the "buffalo hump" while the facial obesity is seen as the typical moon face

Facial plethora hypertension and peripheral edema are common Lability of mood is usually present and occasionally there may be an overt psychosis

Female patients with Cushing's syn

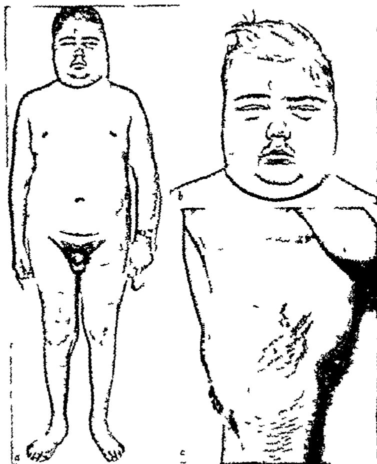


Fig 84 Classic appearance of patient suffering from Cushing's syndrome due to bilateral adrenal hyperplasia Note (a b) the moon facies the truncal obesity and (c) the cutaneous striae over the lower abdomen and hips (R H Williams Textbook of Endocrinology)

patients with Addison's disease and often *only attain an optimal state of well being* on doses of 37 5 to 50 mg per day In addition their requirement for desoxycorti*costerone is considerably more variable* than is the case for patients with Addison's disease

CHRONIC ADRENAL INSUFFICIENCY ASSOCIATED WITH CONGENITAL ADRENAL CORTICAL HYPERPLASIA

Congenital bilateral adrenal cortical hyperplasia causes pseudohermaphroditism in *females and sexual precocity in males* Acute adrenal insufficiency may occur in these instances especially in males It is *characterized by salt loss dehydration and* eventually circulatory collapse More commonly the illness may pursue a subacute *course marked by periods of dehydration* rapid weight loss vomiting diarrhea and abdominal pain usually in association with *intercurrent infections Hypoglycemia ordi*narily does not occur Treatment of acute adrenal insufficiency in these patients is *the same as in other types of adrenal crisis* The use of cortisone in maintenance therapy is discussed below in the section of the adrenogenital syndrome *When corti*sone alone does not control salt loss desoxycorticosterone must be added to the therapeutic regimen

HYPERFUNCTION OF THE ADRENAL CORTEX

The clinical picture of hyperadrenocorticism extends in a broad spectrum from Cushing's syndrome at the one end to the adrenogenital syndrome at the other Cushing's syndrome is the expression of an excessive adrenocortical secretion of the 11 17 oxygenated corticoids hydrocortisone and cortisone while the adrenogenital syndrome is the manifestation of an increased secretion of androgens from the adrenal cortex Between these two extremes there are many patients who present manifesta*tions of each syndrome to a varying degree* Rarely adrenal cortical hyperfunction may be associated with feminization in the *male Twelve such cases have been reported* and all have been due to estrogen producing malignant adrenal cortical tumors

CUSHING'S SYNDROME

This syndrome was first clearly recog*nized by* Harvey Cushing in 1932 While admitting that certain of the cases were due to primary adrenal disease adenoma or *carcinoma* Cushing believed that in those patients with a pituitary basophil adenoma and bilateral adrenal cortical hy*perplasia* (Cushing's disease") the disturbance rested in the anterior pituitary

Etiology Cushing's syndrome represents *the effects of a long continued excessive* secretion of 11 17 oxygenated corticoids hydrocortisone and cortisone by the ad*renal cortex* The adrenal lesion may be adenoma carcinoma or bilateral hyperplasia rarely unilateral hyperplasia may *be found* Much more rarely a tumor in aberrant adrenal cortical tissue (*e g* ovary) may be seen in association with *bilateral atrophy of the adrenal glands* When congenital Cushing's syndrome is almost always associated with bilateral ad*renal hyperplasia When the disease has* its onset during the prepubertal period the adrenal lesion is usually a malignant *tumor In 60 per cent of adult cases bi*lateral adrenal cortical hyperplasia is found in 30 per cent an adenoma or a *carcinoma while in 10 per cent of cases* the adrenal cortices appear normal In many of the patients with normal or hyper*plastic adrenals there is a basophil aden*oma in the anterior pituitary in these cases the primary lesion is believed to be *in the pituitary from which there is in*creased secretion of ACTH

Incidence Cushing's syndrome is a rare *disorder which occurs much* more frequently in the female than in the male Actively secreting adrenal cortical adenomas are practically confined to the female The incidence of the disease is at its peak in the third and fourth decade The syndrome appears to occur particularly frequently following pregnancy

Pathology Bilateral hyperplasia is characterized by symmetrical enlargment of the cortex with increased convolution of the surface Not infrequently a few hyperplastic nodules are present Microscopically the hyperplasia is particularly marked in the zona fasciculata The single and rarely multiple adenomas are well demarcated and surrounded by a narrow *rim of* atrophied cortical tissue Carcinoma of the adrenal cortex is often highly malignant *with spread of the tumor* usually occurring by vein The liver is a frequent site of metastases When a unilateral adenoma or carcinoma is present there is atrophy of the contralateral adrenal cortex due to suppression of the output of ACTH from the anterior pituitary Hyalinization of the basophil cells (Crooke's changes) of the anterior pituitary is invariably present in Cushing's syndrome Similar changes have been observed in *patients who have re*

phils are indications that therapy has been effective

In more seriously ill patients (particularly those with marked mental changes or extensive protein depletion e g severe osteoporosis with fractures) or in those early cases which have failed to respond to roentgen therapy bilateral subtotal or total adrenalectomy is recommended *Bilateral total adrenalectomy* is preferred to prevent the recurrence of hyperadrenocorticism

Adrenal cortical hormone therapy is routinely instituted prior to operation and continued during and after surgery as outlined in the accompanying table In the presence of hypotension Neo-Synephrine or norepinephrine should be given intravenously at a rate sufficient to maintain the blood pressure at normal levels

Patients who have undergone complete bilateral adrenalectomy must be treated in the same manner as are those with Addison s disease Although the availability of hydrocortisone and cortisone has greatly facilitated adrenalectomy in patients with Cushing's syndrome it must be emphasized strongly that these patients are extremely fragile and particularly prone to postoperative complications

Unilateral Adrenal Cortical Adenoma or Carcinoma When Cushing s syndrome is due to an adrenal cortical tumor surgical removal is necessary Because the uninvolved contralateral adrenal cortex is atrophied owing to suppression of ACTH secretion from the anterior pituitary adrenal cortical hormone therapy must be instituted as described for patients undergoing bilateral total adrenalectomy for hyperplasia Within two weeks after surgery the status of the contralateral adrenal cortex is evaluated by the determination of urinary 17 hydroxycorticoids during ACTH administration and rapid tapering of cortisone dosage over a five-day period The ACTH is given daily either in a dose of 20 U S P units by intravenous infusion over an eight hour period or in doses of 80 units of the gel preparation in a single intramuscular injection A gradual rise in the level of urinary 17 hydroxycorticoids during this period indicates that the remaining adrenal gland is functioning adequately The ACTH dosage is then very gradually tapered to allow the inhibited anterior pituitary to return to normal Occasionally irreversible atrophy of the contralateral gland occurs and permanent substitution therapy as for Addison s disease is required

ADRENOGENITAL SYNDROME AND ADRENAL VIRILISM

Apert a French physician introduced the term adrenal virilism in 1910 to designate a syndrome of masculinization in women which he related to alterations in adrenal cortical function Its biological counterpart feminization in the male has since been recognized as an extremely rare condition

Etiology The manifestations of adrenal virilism are due to an increased secretion of androgens from the adrenal cortex The adrenal lesion may be bilateral hyperplasia adenoma or carcinoma Adrenal virilism which is evident at birth is almost invariably due to bilateral hyperplasia When the disease has its onset in later life the lesion is usually a tumor more frequently a carcinoma It is not certain at the present time whether those cases with bilateral hyperplasia are due to a primary anterior pituitary disturbance with an increased secretion of ACTH

Pathology While it is difficult to correlate cytological changes in the adrenal cortex with the type of endocrine disturbance produced it is not uncommon to find in cases of virilization due to bilateral adrenal cortical hyperplasia that the overgrowth is primarily in the zona reticularis The virilizing tumors are frequently highly malignant and metastasize chiefly to the liver and lungs

Clinical Picture As a result of their virilizing properties an increased secretion of adrenal androgens may lead to female pseudohermaphroditism at birth precocious puberty in the preadolescent male and heterosexual development in the preadolescent and adolescent female In addition to their androgenicity these hormones possess a protein anabolic effect Thus while patients with Cushing's syndrome present evidence of protein depletion those with the adrenogenital syndrome show signs of protein conservation e g increased rate of growth in the prepuberal child and increased muscle mass in the adult Heterosexual development in the young female is characterized by hirsutism deepening of the voice absence of breast development enlargement of the clitoris and amenorrhea It must be emphasized that when adrenal virilism is due to bilateral hyperplasia particularly the congenital variety the symptoms and signs of Addison s disease may be present Such patients are particularly prone to develop evidence of salt deficiency

Hormone Therapy Following Complete Adrenalectomy

Preoperatively	Postoperatively
Cortisone acetate 100 mg I M 12 hrs and 2 hrs preop	Day 1—cortisone acetate 50 mg I M q 6 hr
During Operation	Day 2 3—50 mg I M q 8 hr
Hydrocortisone 100 mg I V Repeated 6 and 12 hrs postop	Day 4 5 6 7*—50 mg P O q 12 hr
Cortisone acetate 50 mg I M q 6 hr	Day 8 9 10—25 mg P O q 8 hr
	Thereafter taper cortisone acetate P O slowly to maintenance needs **

* Salt retaining hormone (desoxycorticosterone or fluorohydrocortisone) may be required after day 7

** In patients with severe Cushing s disease and excreting large quantities of 17 hydroxycorticoids into urine it is essential to reduce the cortisone dosage somewhat more slowly than is shown in the table

drome may show signs of masculinization with hirsutism acne deepening of the voice amenorrhea and enlargement of the clitoris In these cases there is probably an increased secretion of androgens as well as hydrocortisone like hormones by the adrenal cortex

The clinical course is characterized by progressive weakness increased susceptibility to infection the symptoms of which are often masked and the appearance of fractures of the spine Death occurs from vascular accidents intercurrent infection or diabetic coma

Diagnosis The combination of marked protein depletion the typical fat distribution and a diminished carbohydrate tolerance strongly favors the diagnosis of Cushing s syndrome Sudden onset suggests an adrenal cortical adenoma or carcinoma an insidious onset favors bilateral hyperplasia

Definitive diagnosis of Cushing s syndrome requires the determination of urinary 17 ketosteroids and 17 hydroxycorticoids The urinary excretion of 17 hydroxycorticoids is almost invariably increased In general the level of 17 ketosteroids is lower than normal in the presence of an adenoma normal or slightly elevated with bilateral hyperplasia and above 30 mg per day when the lesion is a carcinoma of the adrenal cortex Differentiation of these lesions may be considerably helped by study of the patient s response to an eight hour intravenous infusion of ACTH Patients with bilateral hyperplasia tend to show a hyperactive response as measured by rises in urinary 17 ketosteroids and 17 hydroxycorticoids When the lesion is a carcinoma usually no response is observed

In the presence of an elevated level of urinary 17 ketosteroids further help in the differentiation of tumor and bilateral hyperplasia of the adrenal cortex may be obtained by following the urinary 17 ketosteroid excretion during the administration of 9 alpha fluorohydrocortisone 5 to 10 mg daily over a six-day period Patients with bilateral hyperplasia usually show a fall in 17 ketosteroid excretion while those with carcinoma may show no change

Diagnostically helpful laboratory findings are an eosinophil count below 50 per cu mm lymphopenia neutrophilia and polycythemia Glycosuria with diminished carbohydrate tolerance is of frequent occurrence occasionally frank diabetes mellitus may be present In a small number of cases there is a hypokalemic hypochloremic alkalosis Roentgenogram of the sella turcica is almost invariably normal Films of the skull and spine show osteoporosis and compression fractures of the vertebrae may be found An abdominal film may outline an adrenal mass while intravenous pyelograms may reveal depression of the renal shadow Retroperitoneal pneumograms may be of value in the detection of an adrenal mass and the differentiation of adenoma or carcinoma from bilateral hyperplasia

Treatment Whatever the plan for specific therapy it is well to administer potassium chloride 6 gm per day by mouth in the presence of a hypokalemic hypochloremic alkalosis and to combat the protein depletion by the administration of testosterone propionate 25 mg daily by intramuscular injection

Bilateral Adrenal Cortical Hyperplasia When all efforts to detect the presence of an adrenal cortical tumor have failed and bilateral hyperplasia is suspected *pituitary irradiation* may be instituted in those early cases which show minimal signs of protein depletion and only mild psychic involvement A minimum dose of 3000 r should be delivered to the gland Improvement occurs in approximately one quarter of these cases within three months following the commencement of therapy A fall in the titer of urinary 17 hydroxycorticoids and a rise in the level of circulating eosino-

distinguish them histologically from adrenal tumors associated with other syndromes of adrenal hyperfunction Renal arteriosclerosis has been observed as well as hydropic degeneration of renal tubules and degenerative changes in skeletal muscle It has been postulated that the severe potassium depletion observed in these patients is responsible for many of the secondary changes in vital tissues

Physiological Considerations In contrast to the secretion of corticosterone hydrocortisone and the adrenal androgenic steroids aldosterone secretion is not dependent upon ACTH Thus normal levels of aldosterone in the urine may be observed in patients with Simmonds disease or following hypophysectomy Under special circumstances it appears that the secretion of aldosterone may be enhanced by ACTH administration but certainly the baseline secretion of this hormone is not dependent upon ACTH The inability to detect aldosterone in the peripheral blood of patients must make one cautious in the interpretation of the urinary changes in aldosterone level To date both the biological assay method and the physicochemical method of Neher and Wettstein are tedious relatively nonspecific and of limited accuracy It can be readily shown that aldosterone excretion in the urine and presumably aldosterone secretion may be modified rapidly by changes in body hydration and by alteration in sodium or potassium balance Sodium deprivation rapidly leads to increased aldosterone urinary levels This also is observed following the administration of large doses of potassium

Clinical Signs and Symptoms Periodic episodes of muscular weakness dominate the clinical picture These may progress to actual paralysis Muscles of the trunk and extremities are more likely to be affected Those innervated by the cranial nerves are often spared The attacks may be transient or may last for hours to weeks Tetany may be observed Polyuria and polydipsia are prominent symptoms Hypertension hypertensive retinopathy and cardiac enlargement have been present in the majority of instances Edema notably is absent

Laboratory findings include a decreased serum potassium elevated carbon dioxide content depressed serum chloride normal or elevated serum sodium level and an elevated pH of the serum and urine These changes are characteristic of the so-called "hypokalemic metabolic alkalosis" Urinary sodium and potassium concentrations are normal Abnormalities in the electrocardiogram indicative of potassium depletion are almost always present The urinary 17 keto and 17 hydroxy steroid excretion is usually normal whereas urinary aldosterone values are almost always increased

Diagnosis The diagnosis should be suspected in any patient presenting (1) unexplained episodes of muscular weakness (2) tetany with a normal serum calcium (3) diabetes insipidus like syndrome refractory to Pitressin (4) unexplained hypokalemic metabolic alkalosis (5) unexplained "hypokalemic" changes in the cardiogram of a hypertensive nonedematous patient All patients with hypertension and hypokalemia should be checked for possible hyperaldosteronism

Differential Diagnosis (1) Familial periodic paralysis is usually an hereditary disorder It occurs in young persons Between attacks the serum potassium level and muscle function are usually quite normal Obviously hyperaldosteronism may mask as periodic paralysis

(2) Potassium losing nephritis may be due to long standing primary renal disease The presence of marked impairment in renal function such as azotemia suggests primary renal disease rather than the nephropathic changes induced by hyperaldosteronism Undoubtedly some of the cases reported earlier in the literature as cases of "potassium losing nephritis" may have been undiagnosed cases of primary hyperaldosteronism

(3) Tetany due to parathyroid deficiency and hypovitaminosis D can be distinguished by the low serum calcium level In primary aldosteronism tetany is associated with an alkalosis low serum potassium and normal calcium and phosphorus levels

(4) *Secondary hyperaldosteronism* is represented by a group of patients with cardiac renal or hepatic edema in whom elevated levels of aldosterone may be demonstrated These patients characteristically excrete a urine of *low sodium concentration* The pathogenetic significance of the hyperaldosteronism may be investigated by the use of substances such as amphenone which temporarily inhibit the secretion of aldosterone

Treatment The only cure at present for hyperaldosteronism is the removal of the adrenal tumor or bilateral adrenalectomy if the process is not localized Since aldosterone is not an effective inhibitor of ACTH secretion the removal of a tumor in one adrenal does not ordinarily give rise to signs of adrenal insufficiency Since how

At all ages the psychological and social problems associated with this disease must be given careful consideration

Invariably in this condition there is an increased excretion of urinary 17 ketosteroids High values (50 mg per day or more) with an increased proportion of the beta fraction (largely dehydroisoandrosterone) in combination with high levels of urinary estrogens are strongly suggestive of carcinoma of the adrenal cortex as opposed to hyperplasia or adenoma In the presence of congenital adrenocortical hyperplasia the blood ACTH level is high while urinary and blood levels of 17 hydroxycorticoids are low The response of the latter to ACTH is subnormal or absent The presence of a tumor may be detected by means of an abdominal film intravenous pyelography or retroperitoneal pneumography

Differential Diagnosis Sexual precocity in the prepuberal male may be constitutional owing to a pineal tumor to lesions in the hypothalamus or to a Leydig cell tumor of the testes as well as to an adrenal cortical lesion Heterosexual development in the prepubertal or adult female may be caused by a lesion in either the adrenal cortex or the ovary The ovarian lesions include arrhenoblastoma Leydig cell tumor adrenal rests luteoma and polycystic disease (Stein Leventhal syndrome) Differentiation between ovarian and adrenal lesions as the cause of the virilizing syndrome may be helped by following the level of urinary 17 ketosteroids during the administration of fluorohydrocortisone in a dose of 5 to 10 mg daily for five to ten days Dietary sodium should be restricted Should a dramatic fall in urinary 17 ketosteroid excretion occur the causal lesion is presumed to be bilateral adrenal cortical hyperplasia When a persistent depression of the urinary 17 ketosteroid level is not observed it is presumed that the lesion is either an adrenal cortical tumor or ovarian disease In this instance the relatively simple operation of pelvic laparotomy is first performed In the absence of a responsible ovarian lesion the adrenals are then explored

Treatment Treatment of virilizing adrenal cortical tumor is surgical removal In a few cases atrophy of the uninvolved contralateral gland has been found and it is therefore wise in all instances to institute adrenal cortical hormone therapy as described previously for operation on patients with Cushing s syndrome due to tumor When the lesion is a carcinoma with wide spread metastases postoperative x ray therapy is advised but it is usually of little value

When adrenal virilism is associated with bilateral hyperplasia a congenital condition which occasionally goes unnoticed until adulthood the treatment of choice is cortisone suppression of adrenal androgen secretion Therapy is usually initiated with intramuscularly administered hormone at a dosage level of 50 mg per day for older children and 25 mg per day for younger children and infants Thereafter the dose of cortisone should be gradually tapered to that level which gives reasonable suppression of adrenal androgen secretion with minimal untoward side effects of the latter a diminution in the rate of growth is particularly to be watched for For older children maintenance doses of 50 mg of cortisone every other day by intramuscular injection are usually optimal whereas in infants and younger children smaller doses may be quite adequate The amount of orally administered cortisone which is required for maintenance is approximately two to three times as great as that which is effective by the intramuscular route In those cases of bilateral hyperplasia associated with adrenal insufficiency cortisone alone may not control salt loss and desoxycorticosterone must be added to the therapeutic program

HYPERALDOSTERONISM

The isolation in 1952 by Simpson Tait and Bush of a potent sodium retaining factor from adrenal venous blood set the stage for the detection of the clinical syndrome hyperaldosteronism In 1955 Conn described a patient with arterial hypertension polyuria hypokalemia muscular weakness hypochloremia and alkalosis with a high urinary output of aldosterone Removal of an adrenal tumor was followed by amelioration of the signs and symptoms of the syndrome and the disappearance of aldosterone from the urine

Etiology and Pathology The manifestations of the syndrome appear to be due to the metabolic alterations induced by the increased secretion of aldosterone All recorded cases have occurred in adults In nine of these cases an adrenal tumor was found—an adenoma in eight and a carcinoma in one In one case no tumor was discovered and the syndrome was cured following bilateral adrenalectomy Analyses of the tumors have revealed high levels of aldosterone No distinctive structure of these tumors has been found which would

DISEASES OF THE SEX GLANDS

Diseases of the Male Gonads

The two principal functions of the testis are (1) production and nutrition of spermatozoa by the seminiferous tubules and (2) secretion of androgen into the circulation by the interstitial cells of Leydig By virtue of its hormonal secretion the testis promotes development and maintenance of the male accessory reproductive structures and masculine secondary sexual characteristics and in addition exerts a profound effect on body functions apart from those intimately concerned with reproduction

Although there may be discordance between hormonal function and spermatogenesis as is often the case in infertility many disorders of the testis affect both processes

Sex Determination and Sex Differentiation

Recent studies suggest that the diploid cells of man contain 46 chromosomes composed of 44 autosomes and one pair of sex chromosomes (XX in the female and XY in the male) The X chromosome seems to contain the female determining genes and the autosomes the male genic factors Early in the growth of the embryo unequal balance among the sex-determining genes has been postulated to govern differentiation of the bipotential embryonic gonad toward either testis or ovary In the heterozygote male (XY) in contrast to the homozygote female (XX) the single X chromosome is insufficient to overcome the male genic balance of the autosomes Spontaneous and experimentally produced forms of ambisexual development provide evidence that this genetic balance system of sex determination is not absolute and may be modified by various genetic hormonal and environmental factors

Sex differentiation takes place in three steps involving successively (1) the gonad (2) the genital ducts and (3) the urogenital sinus and external genitalia (Fig 85) Normally the pattern of all the sexual structures conforms to the genetic sex established in the zygote at the moment of fertilization

Gonadogenesis The primordial gonad arises in the urogenital ridge from the intermediate mesoderm Early in its development the bipotential primitive gonad (Fig 85) is composed of two unipotential mesodermal primordia each with a distinct physiological as well as morphological capacity (1) a cortical component consisting of the germinal epithelium and (2) a medullary component made up of the primary sex cords (derived from the germinal epithelium) and mesonephric and blastemal elements A third constituent the primordial germ cells which appear to be bipotential arises from an extragonadal site The cortical component can differentiate only as an ovary and the medullary component only as a testis (Fig 85) normally the dominant element follows the genetic sex of the zygote and the recessive element retrogresses

When the gonad destined to become a testis begins to differentiate in a male direction during the seventh to eighth week of embryonic life the cortical component involutes Within the medulla seminiferous tubules form from the primary sex cords and anastomose with the rete testis and testicular ducts and Leydig cells develop Leydig cells proliferate predominantly during the first half of gestation but then gradually involute persisting until shortly after birth

Accessory Sex Structures Fetal castration experiments in placental mammals have thrown light on the embryogenesis of the accessory sex structures Jost and others demonstrated that castration of male fetuses at an early critical period prevented the differentiation of male structures and led to entirely female development of ducts urogenital sinus and external genitalia These studies in the light of recent observations of anomalies of sex in man support the notion that a fetal testicular morphogenetic hormone is essential to pre

ever the status of the second adrenal is not always known it is wise to give supplementary adrenal hormone therapy during and immediately following the operation *i e* 100 mg of hydrocortisone intravenously following the removal of the adrenal and 100 mg of cortisone intramuscularly at the same time The dose of cortisone may be repeated once or twice at intervals of eight to twelve hours

Supplementary potassium therapy *i e* potassium chloride 4 to 8 gm daily should be given preoperatively and postoperatively if tolerated Patients with long standing hyperaldosteronism may have a serious potassium deficit in their tissues The electrocardiogram may be more accurate than the serum potassium level in indicating ultimate tissue restoration of potassium Failure to cure the syndrome may result in death from hypertensive cardiovascular disease Following successful removal of the offending adrenal tissue one may anticipate a restoration toward normal of the blood pressure cardiac size and altered blood and urine chemical values

NONFUNCTIONING ADRENAL CORTICAL TUMORS

Benign nonsecretory cortical adenomas are a frequent finding at autopsy These tumors which are rarely more than 2 to 3 cm in diameter are well circumscribed yellow masses similar in appearance to the normal adrenal cortex They are seen more frequently in middle aged or elderly subjects and in women more often than in men

Nonfunctioning primary adenocarcinomas are extremely rare Unfortunately the tumor is seldom recognized until it is large enough to be palpable or until metastases have occurred It is often mistaken for a kidney and its true character may only be demonstrated by roentgenographic studies (pyelography pneumography) or at operation The tumor must be removed surgically Pre and postoperative replacement therapy such as is essential in patients with functioning adrenal cortical tumors is not necessary in these patients

Carcinomas of the lung and breast frequently metastasize to the adrenal glands Patients with these tumors may occasionally die of adrenal insufficiency induced by such metastases

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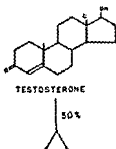
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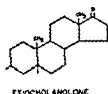
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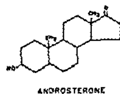


Fig 86

sulfuric acid other tissues play a less important role in its metabolism The major identifiable urinary metabolites are the 17 ketosteroids androsterone and etiocholanolone which are excreted principally as glucuronides (Fig 86) A small amount of testosterone is also transformed into and excreted as estrogen

The testis is under the direct control of the anterior pituitary gland which secretes follicle stimulating hormone (FSH) and interstitial cell stimulating (ICSH) or luteinizing hormone (LH) both of which are glycoproteins FSH stimulates growth of seminiferous tubules and development of spermatozoa Luteinizing hormone induces the Leydig cells to secrete androgen and probably estrogen It has been shown that androgens can also stimulate and maintain spermatogenesis in hypophysectomized animals under certain experimental conditions As is true of many other endocrine glands there is a reciprocal relationship between the hypophysis and the hormonal secretion of the testis The hypothalamus also exerts an effect on the secretion of pituitary gonadotropic hormones as evidenced in man by the association of precocious puberty or sexual infantilism with certain organic lesions of the hypothalamus

It has long been known that doses of testosterone sufficient to reverse signs of androgen deficiency in castrated animals and men frequently fail to reduce the elevated levels of urinary gonadotropin or to reverse the castration changes in the anterior hypophysis This fact led to the detection of a second testicular hormone namely estrogen capable in physiological doses of inhibiting the secretion of gonadotropin There is also indirect evidence that the testis may secrete a third hormone (inhibin" or X hormone) In man destructive lesions or defects involving only the seminiferous tubules are often accompanied by elevated levels of gonadotropin However the mechanism responsible for this rise in FSH excretion remains uncertain

Evaluation of Testicular Function

Clinical Assessment A clinical estimate of the adequacy of androgenic function is obtained by ascertaining the degree of development of the penis and scrotum the size of the prostate the general maturity and status of male secondary sex characters the habitus and skeletal proportions muscular development and potentia Although of great value this method of assessment has limitations Once adult maturation has been attained signs of androgen deficiency are difficult to detect by clinical means even when there is complete loss of Leydig cell function in the mature male (*e g* after castration) regression of secondary sexual characteristics is a slow and selective process Further in addition to disease states which may alter the responsiveness of the target organs to hormone stimulation it is well recognized that there are also racial familial and individual differences in the sensitivity of these structures In this regard the American Indian African Negro and some Orientals have sparse or absent facial and body hair despite normal testicular function

Determination of Urinary 17 Ketosteroids and Androgen It must be emphasized that steroids derived from the adrenal cortex comprise about 80 per cent of the total 17 ketosteroids in urine (and a significant fraction of the androgenic activity) Androsterone (an androgen) and etiocholanolone (a nonandrogenic steroid) the principal urinary metabolites of testosterone are also metabolites of 11-deoxygenated adrenocortical steroids These facts limit the usefulness of measurement of 17 ketosteroid excretion for evaluation of Leydig cell function Testosterone which has an hydroxyl group at carbon atom 17 is not a 17 ketosteroid (Fig 86)

The normal range of 17 ketosteroid excretion in men is 8 to 25 mg per day (mean 15 mg) Prior to puberty only small amounts of 17 ketosteroids and androgen

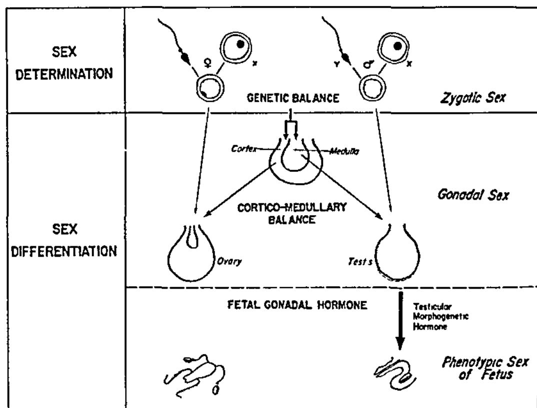


FIG 85 Diagrammatic scheme of human sex determination and differentiation (From Grumbach M M Blanc W A and Engle E T J Clin Endocrinol 17 703 1957)

vent the inherent tendency of the fetus to feminize

Chemistry and Physiology

A wealth of knowledge has firmly established the primary role of testicular hormones (1) in the development and maintenance of the male accessory sex organs—including the penis and scrotum Cowper s and preputial glands—and the secretion of semen and (2) in the development of masculine secondary sexual characters Substances with these properties are called androgens the most potent produced by man is testosterone

All of the properties of testicular androgen are shared by androgenic hormones derived from adrenocortical secretions However in the castrate male the latter are insufficient to prevent eunuchism

It has been assumed since 1935 that testosterone is the principal testicular androgen a contention borne out by the recent isolation of this steroid from human spermatic vein blood From animal experiments in which the seminiferous tubules were destroyed without *affecting* the Leydig cells it has been concluded that testicular androgen originates in the Leydig cells Clinical signs of androgen deficiency are absent in certain testicular disorders in man associated with defective seminiferous tubules but with intact Leydig cells

Recent studies have partially elucidated a pathway for the biosynthesis of testosterone by the testis (see section on Steroid Metabolism) The Leydig cells are capable of synthesizing testosterone from available precursors such as cholesterol and acetate by the enzymatic conversion of these compounds to progesterone and 17 hydroxyprogesterone and then to testosterone and androstenedione There is also good evidence that the testis can convert testosterone to the aromatic steroid estradiol 17β The estrogens estradiol 17β and estrone have been isolated from normal human testes and from testicular tumors Although the adrenal cortex also elaborates estrogens the testis seems to be the principal source in the male Within the testis the site of their formation is still uncertain Both the Leydig cells and the Sertoli cells of the seminiferous tubules have been implicated available evidence favors the former site

The liver is the main site of catabolism of testosterone and of the conjugation of its known metabolites with glucuronic or

mouse units per day Gonadotropin is not detectable in the urine of normal children before the onset of puberty HPG is absent or diminished in hypogonadism secondary to pituitary or hypothalamic disturbances and frequently in chronic debilitating diseases malnutrition and starvation The excretion of HPG is increased in many but not all primary testicular disorders In general elevated levels appear to be related to the degree of damage to the seminiferous tubules

Testicular Biopsy This procedure is of great value in the diagnosis and prognosis of testicular disorders It provides information concerning both the gametogenic and endocrine functions of the testis—the status of the seminiferous tubules and the Leydig cells Biopsy examination of the testis is of use in differentiation of primary and secondary testicular failure in determination of the specific nature of the testicular defect and its prognosis and in distinguishing azoospermia due to obstruction in the passage of sperm from that due to other causes Preferably a specimen should be obtained from each testis

Examination of Semen Specimens of semen for analysis are usually obtained after an interval of 3 days following the last ejaculation The volume of the specimen the number of sperm per ml and the motility and morphology of the sperm are determined

Determination of the Sex Chromatin Pattern Chromosomal sex can be indirectly assessed by cytological methods because of a sexual dimorphism in the nuclear structure of somatic cells first described by Barr et al Preparations suitable for examination can be obtained from smears of buccal mucosa skin biopsy specimens or blood This test is widely used in the investigation of abnormalities of sex differentiation including males with defective testes and azoospermia or severe oligospermia When a female chromatin pattern is detected in a phenotypic male with bilateral testes the test is indicative of a primary testicular disorder congenital in nature (see Klinefelter s syndrome seminiferous tubule dysgenesis)

Response to Chorionic Gonadotropin The effects of human chorionic gonadotropin (HCG) on the immature testis are similar to those of LH It induces differentiation and growth of Leydig cells and the secretion of androgen and estrogen The clinical response to HCG has been used as an ancillary aid in differentiating between primary and secondary hypogonadism

Pubertal Development in the Male

There are wide variations in the age of onset duration and the sequence of events which characterize the biological pattern of male puberty In normal boys signs of puberty may appear at any age between ten and seventeen years the average age of onset is twelve to thirteen years Once initiated the major changes are usually completed or well advanced in three to four years in a small percentage of normal persons adult maturity is not attained until the age of twenty one

A substantial body of evidence suggests that the stimulus for release of pituitary gonadotropin at puberty originates in the hypothalamus and is mediated by a neurohumoral secretion It seems likely that a certain level of physiological maturation presumably including the central nervous system is necessary before this complex and incompletely understood mechanism is activated This level of development is best reflected by the degree of osseous and epiphyseal development (bone age) rather than the chronological age

The sequence of events which marks the pubertal period is initiated by an acceleration in the growth of the testes and scrotum The initial increase in testicular size is largely attributable to changes in the seminiferous tubules which occupy more than 90 per cent of the mass of the testis This phenomenon has suggested to some workers that secretion of FSH precedes that of LH Following the initial acceleration of testicular growth there is an increase in the size of the penis the appearance of pubic hair which has at first a transverse growth gradual enlargement of the prostate and other accessory organs and glands and areolar and subareolar enlargement of the breast

Concomitantly usually between the ages of thirteen and fifteen a marked acceleration of growth takes place involving primarily the skeleton and muscles More subtle changes occur elsewhere The adolescent growth spurt is completed in about three years and in boys accounts for an average increment in height of about 8 inches (4 to 12 inches) and a gain in weight of about 40 pounds Much has been written about the behavioral changes and the psychosexual dynamics of the adolescent period the reader is referred elsewhere for a discussion of this subject

It is necessary that the physician be cognizant of the wide range of normality in the pubertal process in the time of onset

Table 1

ABNORMALITIES OF SEX DIFFERENTIATION

TYPE	SEX CHROMATIN	GONADS	EXTERNAL GENITALIA: PHALLUS	EXTERNAL GENITALIA: LABIOSCROTAL FUSION[3]	GENITAL DUCTS	2 SEXUAL CHARACTERISTICS
FEMALE PSEUDOHERMAPHRODISM						
1 With [illegible]	FEMALE	OVARIES	LARGE	3+–0	FEMALE	PRECOCIOUS MALE
2 Without [illegible] plasia			MEDIUM TO LARGE	3+–1+		FEMALE
MALE PSEUDOHERMAPHRODISM						
1 Sim[illegible] female ([illegible])	MALE	TESTES[1]	SMALL	0–1+	VARIABLE	FEMALE
2 [illegible]			HYPOPLASTIC TO LARGE[2]	1+–3+	PRIMARILY MALE	MALE, ± EUNUCHOID FEMALE
					PRIMARILY FEMALE	USUALLY MALE ± EUNUCHOID
TRUE HERMAPHRODISM	FEMALE > MALE	OVOTESTIS(ES) OR OVARY & TESTIS	VARIABLE		VARIABLE	MALE OR FEMALE
SYNDROME OF GONADAL DYSGENESIS	80% MALE	VESTIGIAL[4] STREAK	FEMALE (RARELY SLIGHT CLITORIDAL ENLARGEMENT)		FEMALE	INFANTILE
SEMINIFEROUS TUBULE DYSGENESIS						
1 [illegible] (Kli[illegible])	FEMALE OR MALE	TESTES	MALE		MALE	MALE ±EUNUCHOID ± GYNECOMASTIA
2 [illegible]						

[illegible] LABIOSCROTAL
2 [illegible] URETHRA
3 DEGREE OF [illegible] 3+
4 [illegible]

are detectable in urine In adult men (and women) there is a gradual fall with advancing age in the amount of 17 ketosteroids and androgen excreted a fall which begins during the third decade The excretion of 17 ketosteroids does not necessarily reflect biological activity determined by animal assay although the results tend to parallel one another For example in men with advanced Addison s disease 17 ketosteroid excretion is markedly diminished but there is only about a 50 per cent reduction in androgen excretion On the other hand in castrate men the diminution in urinary androgen is relatively greater than the decrease in 17 ketosteroids The excretion of 17 ketosteroids is generally reduced in eunuchoidism However the values obtained in such patients may fall within the normal range or occasionally may even reach the upper limits of normal In panhypopituitarism the function of both the testis and the adrenal cortex is impaired and the level of urinary 17 ketosteroids is greatly decreased Low values are also frequently obtained in chronic debilitating diseases and renal insufficiency

Determination of Urinary Estrogen It has recently been suggested by Maddock and Nelson that the increase in urinary estrogen following the administration of chorionic gonadotropin (a placental gonadotropin with luteinizing properties) is a more precise and sensitive index of Leydig cell function than the determination of either 17 ketosteroid or androgen excretion Unfortunately at present there is no simple relatively specific chemical method for this determination in urine

Determination of Urinary Gonadotropin Gonadotropic substances in the urine of normal men and nonpregnant women have been designated in the past as urinary FSH However since the urinary concentrate as prepared for routine bioassay contains a mixture of pituitary gonadotropins Albert has suggested the term HPG (human pituitary gonadotropin) The ratio of FSH to LH in the human male hypophysis is about 1 1 On the other hand male urinary gonadotropin contains relatively more FSH than LH The excretion of gonadotropin (HPG) is not uniform and spontaneous fluctuations in daily output must be considered in evaluating the results of random determinations The normal range of HPG excretion by the mouse uterine weight method of Klinefelter and associates is 6 to 52

tion is described as *constitutional* or *idiopathic precocious puberty* Cerebral lesions particularly tumors accompanied by precocious puberty may affect other hypothalamic functions causing diabetes insipidus bulimia obesity somnolence emotional lability or disturbances in temperature regulation Involvement of the optic nerves or visual pathways causes visual disturbances In some instances signs of puberty precede the onset of detectable neurological involvement and a prolonged period of observation with repeated careful neurological examinations roentgenograms of the skull and determinations of the visual fields is necessary before it is possible to exclude cerebral neoplasm In all varieties of true precocious puberty the excretion of urinary 17 ketosteroids rises slowly to normal adolescent values initially levels between 2 5 and 4 0 mg per day are usually found In contrast to precocious pseudopuberty pituitary gonadotropin (HPG) is excreted in the urine frequently however this is not detectable early in the course

In other forms of isosexual precocity not related to intracranial causes the testes remain more or less immature in contrast to the enlarged phallus and true puberty does not occur Accordingly this type has been called *incomplete sexual precocity* or *precocious pseudopuberty*

The commonest cause of *incomplete sexual precocity* in boys is adrenocortical hyperfunction due to congenital virilizing adrenal hyperplasia or a virilizing adrenocortical tumor This is also the commonest cause of isosexual precocity in males With few exceptions the testes remain prepubertal in size despite enlargement of the penis and scrotum and development of other secondary sexual characteristics An ectopic nodule of hyperplastic adrenal tissue is occasionally palpable in the testis and may be confused with Leydig cell tumor The excretion of 17 ketosteroids is profoundly increased in relation to chronological age and in adrenal hyperplasia an excessive amount of urinary pregnanetriol is detectable (see section on Adrenal Disorders)

Interstitial cell tumor of the testis is an exceedingly rare cause of isosexual precocity In all but two of twenty three reported cases the tumor was unilateral and the contralateral testis was immature Gynecomastia was present in three patients The excretion of 17 ketosteroids varied from 3 to 64 mg per day

Iatrogenic sexual precocity has been produced by the administration of male sex hormone and is seen not infrequently in boys who have been treated with large doses of chorionic gonadotropin for cryptorchidism

Hypogonadism

Testicular insufficiency or hypogonadism is used herein in its broader sense to denote a deficiency of either or both the endocrine and gametogenic functions of the testis Depending upon the nature of the physiological defect hypogonadism can be divided into two groups (1) Hypogonadism secondary to a deficiency of pituitary gonadotropins involving a lack of LH or more commonly both LH and FSH includes disorders characterized by small testes androgen deficiency and absent or low HPG excretion (2) Hypogonadism of primary testicular origin includes disorders accompanied by normal or increased levels of urinary gonadotropin and a variable degree of androgenic function from normal to deficient Of common occurrence are primary lesions of the testis involving *only* spermatogenic function which result in infertility On the other hand when androgenic function is deficient usually but not invariably spermatogenesis is impaired

Androgen Deficiency The clinical signs and effects of androgen deficiency depend upon the age of onset—prepubertal pubertal or postpubertal—and upon the severity and duration of the deficiency

Total loss of testicular androgenic function usually secondary to surgical castration atrophy or congenital defects of the testes before the onset or at an early stage of puberty results in eunuchism in adulthood Hamilton has studied such patients in detail Prepubertal castration is associated with disproportionate growth of the skeleton produced by the delay in epiphyseal closure The span exceeds the measurement for height by several inches and the distance between the symphysis pubis and the sole (lower segment) measures more than 55 per cent of the height Tall stature is common but not invariable (The characteristic skeletal proportions of the eunuch are not pathognomonic and may be found in otherwise normal men) The shoulders tend to be narrow and although the habitus may be lean or obese excessive fat deposition often occurs about the pectoral region

intensity and duration and also of normal variations in the degree of development of the secondary sex characters In normal men the pitch of the voice the size of the external genitalia the amount of body hair and the body habitus all vary from individual to individual and are largely attributable to genetic factors and not to differences in the secretion of testosterone

Delayed Adolescence Commonly failure to undergo sexual maturation by the average age is ascribable to an idiopathic normal variation in pubertal development puberty occurs spontaneously usually by the age of sixteen years but occasionally even later Delayed adolescence although inherently a benign condition is often a severe psychological handicap to the patient and a cause of much anxiety to his parents Many of these boys are short and a delay of several years in osseous development is not uncommon Not infrequently there is a history of late onset of puberty in other members of the family

In addition to idiopathic delay in sexual maturation or pubertal failure or arrest in pubertal development secondary to gonadal or pituitary disease retardation of puberty may be due to inadequate dietary intake and to chronic debilitating illness since these may be associated with diminished secretion of pituitary gonadotropin A rare cause of delayed puberty is previously unsuspected hypothyroidism

Disorders involving the pituitary hypothalamus or testes must be excluded in instances of delayed puberty Roentgenographic examination of the skull and careful examination of the fundi and visual fields are required as well as search for other signs of neurological involvement in all boys who are significantly delayed in their sexual development particularly if this is accompanied by stunting of growth It may be advisable to assess other pituitary functions The diagnosis of hypopituitarism is difficult to establish in this age group in the absence of a demonstrable lesion in the region of the hypophysis A therapeutic trial with chorionic gonadotropin or testosterone may be of value In boys with delayed adolescence sexual maturation frequently continues after the cessation of hormone therapy however in pituitary hypogonadism the induced changes regress

Treatment If a cause of the delayed adolescence is found treatment should be directed toward correction of the basic disturbance (e g measures to improve nutrition surgical removal or irradiation of a pituitary neoplasm) If a lesion involving the hypophysis or testes is detected it is advisable to institute substitution therapy with male sex hormone at about thirteen or fourteen years of age so that the onset of the patient s own puberty coincides with that of his coevals Less well defined is the treatment of boys in whom no apparent etiological factor is found Many will mature spontaneously before seventeen years of age and merely represent an extreme of the normal range Indiscriminate use of hormonal treatment in this group is unwise and a conservative approach is indicated Nonetheless at times psychological considerations may make it expedient to treat such boys A therapeutic trial with human gonadotropin 500 to 1000 I U three times weekly injected intramuscularly or with a testosterone preparation for three to four months frequently initiates the physiological reactions of puberty and maturation will progress after treatment is discontinued

Sexual Precocity

Isosexual precocity in boys is defined as the occurrence of signs of masculinization before the age of ten years Skeletal maturation is accelerated and the epiphyses fuse at a premature age leading to short stature in adult life On the other hand mental and dental development are not precocious Sexual precocity occurs about three times more frequently in girls than in boys The main causes of isosexual precocity in boys can be divided into three groups cerebral adrenocortical and testicular

The cerebral causes of sexual precocity may be functional or organic They are associated with premature activation of the hypothalamic pituitary mechanism and the release of pituitary gonadotropic hormones This form commonly designated *true precocious puberty* or *complete isosexual precocity* is manifested by maturation of the testes and spermatogenesis

Precocious puberty may be caused by organic lesions of the brain either directly or indirectly involving the posterior hypothalamus such as hypothalamic and pineal tumors craniopharyngioma hydrocephalus postencephalitic lesions congenital defects tuberous sclerosis and neurofibromatosis The McCune Albright syndrome of sexual precocity polyostotic fibrous dysplasia and pigmented areas of skin is rare in boys Where no organic cause is found the condi

Treatment The testicular lesion is irreversible If androgen deficiency is present treatment with male sex hormone is effective The gynecomastia is not affected by hormonal treatment and mastectomy may be necessary in some patients for cosmetic reasons

Germinal Aplasia This condition is characterized by seminiferous tubules lined with Sertoli cells little or no tubular fibrosis and absent or rare germinal cells Leydig cell function is usually normal Azoospermia is an invariable finding The testes are normal or moderately reduced in size Urinary gonadotropin may be increased or normal The sex chromatin pattern was male in fifteen out of sixteen patients reported in one study Although it has been suspected that in most instances germinal aplasia is a developmental defect the lesion has also been described following exposure of the testis to ionizing radiation in which case it may be reversible and in some cryptorchid testes

The histopathology and the clinical findings in patients with congenital defects of the testis (testicular dysgenesis) are highly variable Gonadal dysgenesis (in chromosomal males) and male pseudohermaphrodism which are discussed on pages 758 and 759 are other forms of testicular dysgenesis

Anorchia Absence of both testes in phenotypic males is exceedingly rare careful surgical exploration is required to establish the diagnosis Unilateral anorchia is more common and may result from testicular atrophy following herniorraphy or attempted orchiopexy or from a developmental disturbance in which case other anomalies of the genitourinary tract are not uncommon

Infertility In a variety of testicular lesions the defect involves only spermatic function and results in infertility Endocrine manifestations are absent Either the semen lacks sperm or the number or quality of sperm is impaired Testicular biopsy has assumed a major role in differentiating the various disturbances in spermatogenic activity and in determining prognosis Azoospermia is usually associated with severe tubular fibrosis germinal aplasia or spermatogenic arrests and oligospermia with germinal cell desquamation hypospermatogenesis incomplete spermatogenic arrest and less severe forms of tubular fibrosis In most cases the etiology is unknown Azoospermia may also result from obstruction in the excurrent ducts secondary to gonorrhea tuberculosis or a nonspecific infection

Sterility is a common sequel of bilateral cryptorchidism being an almost invariable result of thermal injury to the germinal cells if the testes are not brought into the scrotum before puberty is well advanced It may follow orchitis caused by mumps brucellosis leprosy or occasionally some other severe systemic infection it may result from x ray and other irradiation of the testes or it may be of developmental origin as in seminiferous tubule dysgenesis MacLeod has shown that even relatively minor illnesses may be accompanied by a profound depression in sperm count Starvation and chronic debilitating diseases associated with inanition adversely affect spermatic function Estrogen and large amounts of testosterone will also suppress spermatogenesis

Treatment of Infertility in the Male Although important advances have been made in the evaluation of spermatogenic function treatment of the infertile male is in general both difficult and unsatisfactory Only rarely is it possible to correct the underlying cause The results of therapy of inherent testicular defects in spermatogenesis in noneunuchoidal men by the use of large doses of androgenic steroids gonadotropins pregnenolone thyroid and vitamin preparations have been notably unsuccessful and for all purposes negligible Although testosterone in massive dosage depresses spermatogenesis intermittent treatment with relatively small doses may be of value in some patients with oligospermia Harvey and Jackson have attributed the beneficial effect to more efficient ejaculation and to improvement in the quality of the semen

SECONDARY HYPOGONADISM

Secondary hypogonadism is due to pituitary gonadotropic failure which may result from neoplastic inflammatory traumatic vascular and degenerative lesions involving the hypophysis or hypothalamus such as pituitary adenoma craniopharyngioma astrocytoma infarction carotid aneurysm granulomas especially tuberculosis and histiocytosis (Hand-Christian disease and eosinophilic granuloma) hemochromatosis idiopathic atrophy and developmental defects In many instances including the idiopathic and familial forms the nature of the underlying lesion is not known A functional and reversible depression of gonadotropic activity occurs in malnutrition in

the hips thighs and lower abdomen Muscular development is poor and strength is impaired Except for the appearance of sparse pubic hair secondary sex characters fail to appear and the voice remains juvenile True gynecomastia is commonly present The skin exhibits a characteristic fine wrinkling about the face especially in the perioral and periorbital regions a generalized pale and sallow appearance and increased distensibility Acne and baldness do not occur Sex drive and potentia are absent or markedly reduced The basal metabolic rate is lower in many instances than in normal men In some cases there is anemia usually of a mild degree The erythrocyte sedimentation rate characteristically rises after castration

The effects on somatic and sexual development of partial loss of testicular androgenic function are less striking and vary greatly in degree Characteristic of the milder forms of eunuchoidism are the scant growth of facial hair and a female distribution of pubic hair In men who have attained sexual maturity castration does not result in complete regression of secondary sexual characteristics and the signs of androgen deficiency are less conspicuous The commonest signs are reduction in prostatic size diminished growth of the beard and body hair the appearance of fine wrinkles around the eyes and a pasty sallow complexion Semen volume is reduced Potentia and libido though usually diminished frequently persist Vasomotor phenomena including hot flushes occur occasionally

PRIMARY HYPOGONADISM

(Primary Failure of the Testis)

The problem of classification of primary hypogonadism has not been entirely resolved mainly because the etiology of many of the disorders in this group is uncertain Primary hypogonadism may result from genetic and developmental defects thermal injury as in cryptorchidism trauma destruction and degeneration following orchitis or exposure to ionizing radiation neoplasm and surgical castration Disorders in this group may or may not be accompanied by androgen deficiency although in some eunuchoidism is a constant or frequent feature The excretion of gonadotropin (HPG) is normal or increased depending apparently upon the integrity of the seminiferous tubules

Klinefelter's Syndrome, Seminiferous Tubule Dysgenesis This syndrome described in 1942 by Klinefelter Reifenstein and Albright and later modified by others has recently been a subject of considerable interest and re-evaluation The characteristic features which become apparent during or after puberty include a variable degree of eunuchoidism azoospermia gynecomastia and small testes with atrophy and hyalinization of the seminiferous tubules in which Leydig cells are preserved In most instances the cause is an early developmental defect of the gonad in others the syndrome may be associated with a postnatal lesion

The discovery that some individuals with this syndrome have a female chromatin pattern has served to identify those cases due to anomalous development of the gonad In accordance with this observation and the histopathological characteristics of the testicular lesion the term *seminiferous tubule dysgenesis* has been suggested for this group This affliction is a common cause of primary hypogonadism Of twenty nine patients studied by Grumbach Blanc and Engle nineteen had a female chromatin pattern Although seminiferous tubule dysgenesis may occur in phenotypic males with either female or male nuclei in many instances the cause of Klinefelter's syndrome with a male chromatin pattern is uncertain

The only constant clinical features of seminiferous tubule dysgenesis are infertility and the small size of the testes which are often firmer than normal in most instances testicular atrophy is severe Gynecomastia and eunuchoidism are variable features and when present first appear during the pubertal period Hypospadias and cryptorchidism have been observed infrequently Mental retardation is not uncommon This disorder has also been reported in association with myotonia dystrophica

The excretion of urinary gonadotropin is usually but not invariably increased In general urinary 17 ketosteroids are within the normal range

Although the etiology of seminiferous tubule dysgenesis has not been established the occurrence of this affliction in families and in identical twins favors genetic predisposition as a factor It has been postulated that in the chromosomal females the defect results in failure of the cortical component of the primordial gonad to develop and to suppress the medullary component (Fig 85) As a consequence the gonad chromosomally destined to become an ovary differentiates as a testis albeit a defective one

Treatment of Androgen Deficiency

The most useful substances for the treatment of androgen deficiency are the preparations of testosterone which are available in forms suitable for intramuscular oral and buccal or sublingual administration or as pellets for subcutaneous implantation The mode of administration depends for the most part on the preference of the patient and the cost

Esterification of testosterone with organic acids potentiates its activity when injected as an oily solution Testosterone propionate in doses of 25 to 50 mg by intramuscular injection twice or three times weekly is usually adequate for replacement therapy However longer acting esters are available which can be administered less frequently One dose of 200 to 400 mg of testosterone cyclopentylpropionate or testosterone enanthate is highly effective when injected at three to four week intervals

Methyltestosterone is an effective preparation for oral and buccal or sublingual use It is usually administered in doses of 50 mg (30 to 75 mg) per day orally or about 25 mg per day by sublingual absorption It is not a natural compound and its metabolism differs from that of testosterone Administration of the 17 methylated derivative does not cause an increase in 17 ketosteroid excretion in addition although a potent anabolic steroid it frequently produces creatinuria rather than retention of creatine

Pellets of testosterone implanted subcutaneously provide an efficient and economical method of administration Implantation of 750 to 1000 mg usually suffices for four to six months However patients usually prefer one of the slowly absorbed intramuscular preparations when a sustained androgenic effect is desirable

No potent protein anabolic steroid lacking androgenic properties in man is available at present although intensive efforts have been made to obtain one

Undesirable Effects These include edema due to retention of extracellular electrolyte (an uncommon effect except with use of large doses or in elderly persons with diminished cardiac reserve) acne gynecomastia depression of spermatogenesis in some fertile men when administered in large doses masculinization in women and premature closure of the epiphyses Rarely methyltestosterone causes intrahepatic cholestatic jaundice

Androgen therapy is contraindicated in patients with carcinoma of the prostate

Cryptorchidism

The terms "cryptorchidism" and "undescended testes" are used synonymously to designate testes which have never descended into the scrotum Unilateral cryptorchidism is approximately four times as common as bilaterally undescended testes A cryptorchid testis may be situated in the abdomen within the inguinal canal or in an ectopic position outside the scrotum and the normal pathway of descent The majority of undescended testes are inguinal To avoid needless treatment it is essential to distinguish this condition from *migratory or retractile testes* which lie in the lower or upper scrotum and with the slightest stimulus are withdrawn into the inguinal region and occasionally into the abdomen by contraction of the cremasteric muscles

The testes usually descend into the scrotum at about the eighth fetal month occasionally descent is delayed until or shortly after birth Incomplete descent is common in premature male infants Scorer found undescended testes at birth in 3 4 per cent of 1500 full term male infants during the first month of life 50 per cent of the undescended testes reached the scrotum In a prospective study of the incidence of congenital anomalies by McIntosh and associates only 0 5 per cent of 2793 live born male infants had undescended testes at 12 months of age The incidence of unilateral and bilateral cryptorchidism in large series of adult males has been variously estimated at 0 2 to 0 4 per cent Spontaneous descent occurs frequently during the first year of life It is probably less common after this age than was previously supposed

The etiology is incompletely understood Maldescent may be due to mechanical abnormalities which deter the passage of an otherwise normal testis or to imperfect development of the testis attributable to an inherent testicular defect or to a deficiency of gonadotropin Pecent studies indicate that testicular dysgenesis is an important etiological factor In rare instances unilateral or bilateral cryptorchidism is the only anatomical abnormality of the external genitalia in individuals with intersexuality

Diagnosis The most difficult aspect of diagnosis is distinguishing the true unde

chronic disease states associated with inanition and nutritional deficiencies and in some patients with myxedema High concentrations of androgen as in the adrenogenital syndrome may cause secondary hypogonadism Excess estrogen either from ingestion or from an endogenous source such as a feminizing adrenal tumor depresses the secretion of pituitary gonadotropin The testicular atrophy and gynecomastia which occur in some patients with severe liver disease have been ascribed by some to increased levels of estrogen due to impaired hepatic degradation of these steroids Irrespective of etiology *in almost all instances of secondary hypogonadism urinary gonadotropin is absent or markedly diminished*

The deficiency of pituitary gonadotropic function occurs either as an isolated defect (hypogonadotropic eunuchoidism pituitary hypogonadism) or in association with a deficiency of other hormones of the anterior pituitary (hypopituitarism) On the other hand hypoadrenalism or hypothyroidism secondary to pituitary failure rarely is found without concurrent involvement of gonadotropic function and secondary hypogonadism In some instances only the secretion of LH is impaired Albert et al have termed this partial gonadotropic failure In any event secondary hypogonadism is always accompanied by inadequate androgenic function of the testes and with rare exceptions absent or deficient spermatogenesis

The clinical manifestations vary with age of onset degree of the deficiency and whether there is coexistent deficiency of other anterior pituitary hormones Hypopituitarism occurring during childhood commonly designated pituitary dwarfism results in proportionate dwarfism and complete sexual infantilism The characteristic features of prepubertal or pubertal gonadotropic failure (hypogonadotropic eunuchoidism) occurring as a selective pituitary deficiency include a eunuchoid habitus small testes lack of development of secondary sexual characteristics absence of urinary gonadotropin and low 17 ketosteroid excretion The absence of gynecomastia regarded by some as a salient feature is of doubtful clinical value in differentiating primary from secondary hypogonadism Deposition of fat in the pectoral region is common and at times may be difficult to distinguish from true gynecomastia Isolated pituitary hypogonadism is relatively rare in adult men a more frequent occurrence is a variable degree of panhypopituitarism (see section on Pituitary Diseases)

It is essential in all instances to obtain roentgenograms of the sella turcica and to plot the visual fields Testicular biopsy is useful but considerable experience is necessary for adequate interpretation When hypogonadism is accompanied by adrenal insufficiency the excretion of 17 ketosteroids is usually less than 3 0 mg per day a level significantly below that found in castrate men As previously emphasized urinary gonadotropin is absent (less than 6 mouse units)

McCullagh and his associates were the first to describe a group of eunuchoidal men with relatively intact spermatogenic function whom they termed *fertile eunuchs* The size of the testes were normal or only moderately reduced Leydig cells were absent or hypoplastic and androgen deficiency was always present Urinary gonadotropin (largely FSH) was excreted in normal but not increased amounts Some cases appear to be due to a selective deficiency of LH in others the primary defect may be testicular in origin The response to chorionic gonadotropin has been variable Similar findings have been reported by Albert in a patient with arrest of puberty caused by a pituitary tumor

The pathogenesis of testicular atrophy which follows traumatic injury to the spinal cord is uncertain Both primary and secondary hypogonadism have been described in the Lawrence Moon Biedl syndrome

Treatment A physiological approach to the treatment of secondary hypogonadism necessitates the use of gonadotropin therapy Unfortunately FSH preparations derived from animal sources are not consistently effective and when repeatedly injected stimulate immunological mechanisms which reduce the hormones effect Chorionic gonadotropin obtained for commercial use from human pregnancy urine stimulates the Leydig cells to secrete androgen but must be administered at frequent intervals (three to four times a week) It does not have a direct effect on the seminiferous tubules although in a few instances of partial gonadotropic failure spermatogenic as well as Leydig cell function improved after its use Because long continued administration of chorionic gonadotropin is expensive and in general impractical substitution therapy with a testosterone preparation is usually advisable and effectively corrects the deficiency of androgen

from prolonged stimulation by chorionic gonadotropin To minimize this risk Robinson and Engle recommend a short intensive course of 4000 units of chorionic gonadotropin administered intramuscularly daily for three days Hormonal treatment is contraindicated when the testis is ectopic or associated with a hernia

If the undescended testis is atrophic and biopsy examination at the time of surgery shows irreversible changes it is generally advisable to perform orchiectomy provided the contralateral testis is in the scrotum This also applies to a testis which despite all attempts at mobilization cannot be brought into the scrotum

Impotence

Impotence is a complicated problem which may be either relative or complete and may involve any phase of the sexual act Although it is a symptom of androgen deficiency and of genitourinary or neurological disease in many instances it is psychic in origin When impotence is the principal complaint of a patient it is usually the result of an emotional disturbance in which case androgen therapy is valueless and at times may add to the psychic trauma Ganglion blocking agents as used in the therapy of hypertension are also a notable cause of impotence

Male Climacteric

The spontaneous occurrence of a male climacteric is still controversial Although in women during the fifth decade ovarian failure *and a compensatory rise in gonado*tropin excretion is an anticipated and physiological accompaniment of the aging process spontaneous testicular deficiency of sufficient degree to produce symptoms is an exceedingly rare occurrence Many of the symptoms ascribed to this syndrome are common in psychoneurotic syndromes in middle aged and elderly men The diagnosis should be documented by finding an increased excretion of gonadotropin and by testicular biopsy and confirmed by obtaining a therapeutic response to androgen therapy but not to placebos

Orchitis

Acute orchitis a common complication of mumps is a rare occurrence in the course of other specific infectious diseases Mumps orchitis infrequent before puberty occurs in *18 to 43 per cent of cases of* mumps in postpubertal males usually five to seven days after the onset of parotitis Involvement of the salivary glands is not invariably present Testicular involvement is bilateral in about 20 per cent of cases of mumps orchitis The orchitis is manifested by high fever and a swollen tense painful exquisitely tender testis Concurrent epididymitis is common The acute symptoms *usually persist for three to four days the* orchitis in general subsides in seven to ten days As a result of inflammation and edema of the testis conspicuous atrophy occurs in about 50 per cent of the cases and sterility in an undetermined number of instances In treatment of mumps orchitis cortisone and related steroids have been used in large doses with encouraging results Symptomatic relief has been prompt *in most instances but the effect of corti*costeroid therapy on the incidence of testicular atrophy and infertility remains to be determined

Chronic orchitis is associated with painless hard sometimes nodular enlargement of the testis Syphilis the most common cause may produce an interstitial orchitis in which the testis is characteristically smooth and wooden in consistency ("billiard ball" testis) involvement is frequently bilateral Other causes include tuberculosis leprosy brucellosis glanders and certain parasitic infections such as filariasis and bilharziasis

Tumors of Testis

Tumors of the testis are uncommon comprising about 2 per cent of all forms of cancer in the male and frequently are malignant The greatest incidence occurs in the third and fourth decades Testicular tumors may arise from any of the cellular components of the testis or their embryonal precursors

Considerable uncertainty applies to classification especially of those new growths whose origin has been ascribed to the potentially totipotent germ cell Melicow has suggested the following classification

scended testis from the more common retractile testis of childhood repeated examinations may be necessary especially in obese boys It is *important to ascertain by* careful inquiry whether the testis at any time has been observed in the scrotum In cryptorchidism the homolateral side of the scrotum is empty and poorly developed The *patient should be carefully examined* in the erect and recumbent positions in a warm room and with warm hands Bimanual examination and palpation while the patient performs the Valsalva maneuver or *while the examiner applies pressure to the* lower abdomen are useful procedures In boys with retractile testes elicitation of the cremasteric reflex often results in a localized puckering of the scrotal skin *If the testis is palpated in the normal pathway of* descent gentle manipulation should be used in an attempt to displace it into the scrotum Such mobile testes do not require therapy and will remain in the scrotum *with the advent of puberty Failure to pal*pate a testis on multiple occasions suggests that the testis is intra abdominal atrophic or absent However spontaneous descent may subsequently occur even in instances *in which the testis is not felt*

Treatment The treatment of undescended testes is a vexing and controversial subject experienced observers differ in their approach to the problem Though opinions *are strong there are too many gaps in our* knowledge to justify dogmatism Major considerations are (1) the potential fertility of the undescended testis (2) the likelihood of spontaneous descent and (3) the propensity of the undescended testis to undergo malignant change

It is well established that during or after puberty the undescended testis shows degenerative changes which eventually proceed to atrophy With good reason these changes have been ascribed to the deleterious effect of the higher temperature of an extrascrotal environment on the testis especially on the germinal epithelium The tubules gradually undergo progressive fibrosis and loss of germinal elements although androgenic function may persist for many years Almost all *men* with bilateral undescended testes are sterile However general agreement is lacking as to the age at which the fertility potential of *the cryptorchid* testis is impaired Although Nelson and Robinson and Engle and others have observed a lag in development of the seminiferous tubules and in some instances a mild degree of *fibrosis in* testes retained after the age of six to ten years the significance of these changes is uncertain after puberty irreversible degenerative changes *frequently take place*

The incidence of cancer in undescended testes is considerably greater than in scrotal testes and more so in abdominal than inguinal testes Although precise statistics are *not available the over all risk appears to* be small with the exception of the dysgenetic frequently undescended gonads of intersexes which are especially prone to malignant degeneration

*The most important problem in the treat*ment of patients with cryptorchidism is the age at which it is advisable to attempt correction Treatment consists of orchi*opexy or of the administration of chorionic gonadotropin followed by orchiopexy* when necessary It is generally agreed that therapy must be instituted before puberty is advanced if irreparable testicular damage is to be prevented but opinions differ in *regard to the optimal age for treatment* In the more common unilateral cryptorchid the scrotal testis if normal is adequate for fertility Treatment is recommended for cosmetic reasons to facilitate examination *for neoplasm and as additional* insurance against infertility in the event the scrotal testis is defective or impaired at a later age In bilateral cryptorchidism preservation of fertility is the major consideration Here the risk of damage to the testis by orchiopexy which even in experienced hands is not negligible must be weighed against the possibility of infertility if surgical treatment is delayed too long When bilateral orchiopexy is followed by atrophy of the testes the patient will be eunuchoid as well as sterile Since the majority of undescended testes descend before puberty the writer believes it is justifiable to delay treatment until nine to eleven years of age unless the testis is ectopic or associated with a hernia

Many workers recommend a course of treatment with chorionic gonadotropin before orchiopexy In some cases hormonal therapy is effective and *orchiopexy is un*necessary It is the opinion of most that testes which descend with such therapy would have descended spontaneously at puberty under the stimulus of endogenous *gonadotropin* Testes which fail to descend are either inherently defective or mechanically retained Some experienced workers are of the view that hormonal treatment should not be used for long periods because of the possibility of damage to the testis

dites when the gonads are ovaries and true hermaphrodites when both ovarian and testicular tissue are present The application of nuclear tests of chromosomal sex has brought to light two additional forms of intersexuality namely gonadal dysgenesis in chromosomal males and seminiferous tubule dysgenesis (Klinefelter s syndrome) in chromosomal females In both instances the gonads are defective or absent and there is discordance between chromosomal sex as determined by nuclear morphology and somatic sexual development (phenotypic sex) Persons with postnatal viriliza tion or feminization or with psychiatric disorders such as homosexuality are not included among abnormalities of sex differ entiation

Anomalies of sex are not exceedingly rare and may result from genetic defects or from deleterious environmental factors In many forms the etiology is still uncertain

The syndrome of gonadal dysgenesis (ovarian agenesis Turner s syndrome Bonnevie Ullrich syndrome) is manifested in its typical form by female but infantile development of the accessory sex structures including the external genitalia short stature a characteristic habitus and multiple congenital defects The most common associated anomalies include webbed neck coarctation of the aorta lymphedema of the extremities and ocular skeletal and renal defects No true gonad is present as such in each mesosalpinx there is a ridge of connective tissue devoid of ova follicles or seminiferous tubules Except for the development of some pubic and axillary hair (in contrast to hypopituitary dwarfs) no secondary sexual development occurs and these patients remain sexually infantile The titer of urinary gonadotropin is increased but rarely before nine years of age A male chromatin pattern has been found in about 80 per cent of patients with this syndrome and is of diagnostic significance A number of variant forms have been described rarely the clitoris is enlarged Therapy is directed toward the correction of sexual infantilism (see Disorders of Ovary) and remediable congenital anomalies

Seminiferous tubule dysgenesis is discussed on page 752

The management of patients with ambisexual development is greatly facilitated by early diagnosis infants with anomalous development of the external genitalia deserve prompt investigation The reader is referred to the publications of Wilkins Money Hampson Grumbach and others for detailed discussions of diagnostic therapeutic and theoretical considerations and for additional references

MELVIN M GRUMBACH

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Diseases of the Female Gonads

The human ovary has a dual physiological responsibility (1) the development and production of ova and (2) the elaboration of at least two hormones estrogen and progesterone and probably a third hormone relaxin

The time of greatest ovarian activity is between the menarche and the menopause Activity before the menarche or after the menopause and lack or aberration of activity between these events represent pathological ovarian function This may be due to (1) abnormal stimulation of the ovary by other glands (2) end organ disease (3)

- A Primary tumors
  - I Germinal
    - 1 Pure seminoma
    - 2 Embryonal tumors
      - a Embryoma
      - b Choriocarcinoma
      - c Embryonal carcinoma
      - d Teratocarcinoma
      - e Adult teratoma
    - 3 Combinations of 1 and 2 and of the various types of embryonal tumors
  - II Nongerminal tumors
    - 1 *Interstitial cell tumor*
    - 2 Sertoli cell tumor
    - 3 Tumors of testicular stroma fibroma lipoma etc
- B Secondary tumors
  - I Lymphoma plasmacytoma leukemia etc
  - II Metastatic carcinoma

Germinal Tumors Most common are germinal tumors and of these *seminoma* exceeds in frequency all other testicular tumors Seminoma although usually fairly uniform in cellular architecture may contain embryonal elements such as chorionic syncytium in the primary growth or in metastatic lesions In contrast to the embryonal tumors which tend to invade the spermatic cord and to metastasize early especially to lung seminomas in general are relatively slow growing and commonly invade the iliac and periaortic lymph nodes before generalized dissemination is demonstrable In addition seminomas are frequently highly radiosensitive whereas embryonal tumors are usually resistant to radiotherapy The significantly increased incidence of germinal tumors particularly seminoma in undescended testes and in the dysgenetic gonads of intersexes has been discussed above

Many patients with germinal tumors excrete increased amounts of urinary gonadotropin The gonadotropin may be pituitary in origin (HPG) and may show principally FSH activity on bioassay or it may originate from tumor tissue in which event chorionic gonadotropin (HCG) is detectable in the urine Increased excretion of HPG is usually found in association with seminoma The significance of this association is not clear but it may reflect the increased incidence of this tumor in patients with certain inherent testicular defects Excretion of chorionic gonadotropin is most frequently associated with embryonal tumors especially choriocarcinoma However neither increased levels of HPG nor detectable amounts of HCG are consistently found in patients with germinal tumors even when the involvement is widespread nor is one type of gonadotropin invariably associated with either seminoma or the embryonal tumors

Interstitial Cell Tumors Tumors of this type are rare occur at any age and are usually but not invariably benign In boys interstitial cell tumors cause sexual precocity but not true puberty since spermatogenesis is absent Their only recognizable endocrine manifestation in the adult is gynecomastia which has been observed in about 10 per cent of cases

Clinical Symptoms and Signs The most common and characteristic symptom is painless and frequently rapid enlargement of the testis The swelling is firm diffuse and symmetrical in most instances but may be nodular Occasionally there is dull dragging inguinal pain and rarely flank pain which has been attributed to involvement of the periaortic lymph nodes Attachment of the testis to the scrotal skin is rare The iliac inguinal and femoral lymph nodes may be enlarged metastasis to a deep cervical node is sometimes found Occasionally tumors of the testis are associated with a coincident hydrocele Gynecomastia may occur with germinal or interstitial cell tumors

Tumor must be differentiated from tuberculosis from syphilitic orchitis from other forms of acute and chronic epididymo orchitis and from hydrocele spermatocele and adenomatoid tumor of the epididymis

Management The treatment is surgical removal of the involved testis and depending upon the nature of the tumor radical resection of regional lymph nodes and ir radiation The five year survival rate for seminoma is greater than 75 per cent The mortality rate is high for other germinal tumors with the exception of adult teratoma

Hermaphrodism

(Intersexuality)

These terms are commonly used to designate a group of congenital abnormalities characterized by a variable degree of ambisexual differentiation of the accessory sexual structures and gonads of one or both sexes Intersexes may be further subdivided depending upon the sex of the gonad into male pseudohermaphrodites when the gonads are testes female pseudohermaphro

Should investigation and possible exploration prove entirely negative it must be assumed that the child has developed a physiological sexual cycle at an earlier than normal age and that no treatment is possible or necessary

From a physiological point of view precocious puberty of this type is apparently harmless A number of cases followed by Novak throughout their active sexual years proved to be normally reproductive and became menopausal at a normal age

Emotionally and socially however children of this type present a serious problem because they are not only distinctly different from their contemporaries but also not sufficiently mature emotionally to cope with the sexual drive which inevitably results *from estrogen production That they are* actually reproductive at this age has been demonstrated many times (75 primipara under thirteen years of age were reported from the University of Arkansas Medical Center for instance) but possibly most dramatically by the now famous case of Lena Medina the Peruvian girl who was delivered of a normal child by cesarean section at the age of five years and eight months Sections of the ovaries taken at the time of cesarean section disclosed old corpora lutea and corpora albicantia which indicated that she had been ovulating for a considerable length of time

Parenthetically in this era when estrogen tablets are not infrequently found in the family medicine chest it should be observed that the age-old tendency of children to experiment with pill swallowing has resulted in the occurrence of precocious uterine bleeding as a result of exogenous estrogen stimulation Cases of this type seen by the author as well as those reported by Cook and others have not however had evidence of the development of other secondary sex characteristics and their episodes of vaginal bleeding have been very irregular and sporadic

The other possible abnormality of the menarche *i e* delayed onset of menstruation is much more frequent and its etiological factor or factors more difficult to identify and treat

Apprehension concerning delayed menarche is more often expressed by mothers than by the patients themselves and it is most important to carry out a thorough history physical examination and laboratory investigation before stating to the mother and daughter that this is merely a physiological delay Aside from the usual routine of history taking emphasis should be placed on ascertaining when other secondary sex characteristics developed on whether the patient has ever had any systemic ailments and on a careful inquiry into the patient s emotional environmental and familial status

In order to eliminate the possibility of congenital abnormality of the female genital tract as an etiological factor it is most important to carry out a thorough examination of the external genitalia followed by a vaginal examination or should the condition of the hymen not permit it a careful rectal examination Not infrequently girls in their late teens who subsequently have been found to have some developmental abnormality of the genital tract which has made menstruation for them impossible *have been extensively treated with hormone* therapy in attempts to bring on menstruation

These congenital abnormalities may occur anywhere along the genital tract A rare but significant developmental abnormality is complete fusion of the hymeneal ring which prevents egress of menstrual fluid even though the patient may be going through cyclic episodes of uterine bleeding This process produces hematocolpos and hematometra which occasionally reach such proportions that the uterus can be easily palpated suprapubically and also produces periodic episodes of fairly severe lower abdominal discomfort and cramps at the time when the patient is actually having occult menstruation This condition is easily identified by local examination Incision under local or general anesthesia results in a satisfactory cure

Absence of the uterus in the presence of intact ovaries is also rare It is identified not only by physical examination but also by the presence of other secondary sex characteristics whereas congenital absence of the ovary with or without the presence of the uterus has as one of its characteristics no indication of sexual development of any kind Occasionally cases of ovarian agenesis are seen however with a moderate amount of breast development and pubic and axillary hair growth This evidence of estrogen activity probably results either from estrogen produced by the adrenal or from exogenous estrogen which the patient has received therapeutically elsewhere but of which she is unaware In all cases of suspected ovarian agenesis at least two separate twenty four hour urine specimens should be obtained for a determination of urinary gonadotrophin excretion A high or "menopausal level of uri

ovarian disease or neoplasm or (4) systemic pathology

Evidence of ovarian function is provided by observation of the development and activity of secondary sex organs such as the breast and the internal and external genitalia Ovarian hormone production develops the latent existing characteristics of femaleness and combined with ovum production provides the organism with the essential characteristics of being a female Both of these essential ovarian processes are triggered by gonadotrophin secretion from the pituitary gland Under normal circumstances ovarian hormone activity is probably most graphically expressed in the periodic phenomenon of menstruation

Therefore any abnormality of secondary sex development or physiological function represents either a pathological organ or a pathological stimulus The ovary may be normal but may receive abnormal hormonal stimulus or none at all or its own normal hormonal secretion may be ineffective because a pathological condition of the target organ prevents the latter from being receptive With this in mind the causes of aberrations of ovarian function in different age groups can be reasonably identified by a systematic search using available diagnostic techniques for the offending unit in the hormonal chain Once the source of the difficulty is identified and only at this time can the patient be rationally treated

Menarche

The menarche or onset of menstrual function in the human occurs with greatest frequency at the age of twelve or thirteen but there is a wide latitude in the time of its physiological onset When menstruation begins before the age of ten or after the age of fifteen a decision must be made whether the precocious or delayed menarche is a physiological variant or whether it is due to some anatomical glandular or systemic abnormality

Cases of precocious menstruation even at the age of three or four have been reported by Novak in which no pathological abnormalities could be identified either hormonally or surgically although rare and bizarre diseases may be etiological factors Idiopathic precocious menstruation however is almost invariably accompanied by other secondary sex characteristics and is a condition naturally suspected of accumulating estrogen from an abnormal source Possible abnormal sources of estrogen production are functioning tumors of the ovary or adrenal or some abnormal pituitary stimulus Novak found that over 90 per cent of his cases were idiopathic or physiological

Such conditions must be searched for by rectal examination under anesthesia laboratory assay of adrenal function and sella turcica x ray Since estrogen production is obvious it need neither be searched for nor measured but the difference between the hormonal activity of a functioning ovarian tumor and a normal but precociously stimulated ovary can sometimes be identified by determining the presence or absence of ovulation If the precocious menstruation has any degree of regularity a twenty four hour urine specimen may be obtained premenstrually for pregnandiol determination Should this excretion product of progesterone be present it is an indication that ovulation has occurred a phenomenon which would not be present in the presence of a functioning ovarian tumor This is therefore a good indication that the ovary is precociously stimulated by gonadotrophin either from a pituitary tumor or because the process of growth in the individual has proceeded so rapidly that the pituitary gland has started its gonadotrophic function several years sooner than usual Other means for determining ovulation such as endometrial biopsy and basal body temperature are not considered practical in this age group It must be remembered that the absence of evidence of ovulation does not necessarily mean the presence of a functioning ovarian tumor because an ovary especially at the time of the menarche may be sufficiently stimulated to produce estrogen but not to ovulate

Surprisingly small tumors of the ovary may produce sufficiently large amounts of estrogen to accomplish secondary sex development and function Therefore unless the examiner is reasonably sure that rectal examination under anesthesia discloses no ovarian enlargement surgical exploration of the pelvis should be carried out

Cortical hyperplasia or tumor of the adrenal which may cause precocious menstruation is usually accompanied by other signs of aberrant sexual development such as hirsutism and a search for abnormal steroid excretion should be instituted Pituitary tumors which produce precocious menstruation may also have other local or systemic symptomatology (*q v*) as well as abnormal x ray findings

the patient actual evidence that it is possible for her to menstruate There is a possibility that the pituitary and subsequent ovarian depression produced by estrogen administration may result in a physiological rebound phenomenon following therapy resulting in a surge of gonadotrophin production and subsequent spontaneous menstrual activity but this is purely theoretical

Ovarian Abnormalities During Active Menstrual Life

Probably the most delicate and certainly the most frequent indicator of aberration in ovarian function is the occurrence of some change in the menstrual process Although alterations in the occurrence frequency amount and length of menstrual bleeding may be caused by many types of local or systemic pathology it is nevertheless true that ovarian dysfunction has as its most sensitive "ovimeter" changes in menstrual function which may be called dysmenstruation" (if we may be allowed to coin a generic word to represent any type of menstrual abnormality) *

The ovary of course is subject to a variety of disorders—infectious neoplastic degenerative possibly metabolic—but this section is mainly concerned with the hormonal physiology and pathology of the ovary Various types of ovarian tumors also produce ovarian hormonal malfunction and for a thorough discussion of this type of ovarian abnormality the reader is referred to the recent extensive monograph by Morris and Scully

Dysmenstruation thought to be due to ovarian hormonal abnormalities is classified under various names By some these are considered to be "functional" menstrual disorders the implication presumably being that they occur in the absence of any recognizable local or systemic pathological conditions and are therefore not "organic Others prefer to call these disorders "dysfunctional" the implication being that normal menstruation is "functional and therefore any abnormality in menstruation should be considered dysfunctional Regardless of the semantics involved the present discussion concerns hormonal aberrations of ovarian function of which dysmenstruation is the most frequent symptom Other symptoms of ovarian hormonal malfunction may be obesity hirsutism vasomotor instability and infertility but if these symptoms are in fact due to ovarian endocrine disease they are also accompanied by menstrual aberrations

Therefore when a patient complains of any sort of dysmenstruation an effort must be made to determine whether this symptom is due to ovarian dysfunction or whether it has some other physiological or pathological cause Although dysmenstruation is an almost invariable indicator of ovarian dysfunction it must not be assumed that this is the only cause Therefore *before any treatment is instituted* other causative factors must be considered and ruled out by a process of elimination A possibly oversimplified check list for this process might be similar to that listed below

Such a simple check list does not take into account the rare situations in which endometrial carcinoma may occur coinci

* An expression used for the same purpose by Buxton and Southam Human Infertility New York Paul B Hoeber Inc 1958

Symptom—Amenorrhea

Cause—Physiological		Before menarche After menopause Pregnancy Lactation
	Congenital	Absence of one or more genital organs
	Psychological or Environmental	
	Pathological	System c disease including thyroid or adrenal disease

Symptom—M norrhagia and Metrorrhagia

Cause—Local disease		Neoplastic—benign or malignant—carcinoma of cervix or corpus polyps adenomyomata fibromyomata etc Trophoblastic abnormalities—any pregnancy abnormalities which cause bleeding Inflammatory reactions—vagina cervix uterus tubes ovaries *pelvis* in general
	Systemic disease	Blood dyscrasias chronic debilitating disease thyroid or adrenal abnormalities
	Psych atric	

nary gonadotrophin excretion is an indication of either complete absence of ovarian tissue or ovarian tissue which has been so destroyed by some pathological change that it is unresponsive to gonadotrophin stimulation

In the event that no congenital abnormalities are identified and the investigator is reasonably certain that ovarian tissue is present thorough physical and laboratory examination must be carried out to eliminate the possibility of abnormalities of other endocrine glands or of systemic disease The presence of masculinizing characteristics such as hirsutism unusual development of skeletal musculature or voice changes leads one to suspect the presence of functioning ovarian adrenal or pituitary tumor or of adrenal cortical hyperplasia These conditions will be discussed in subsequent paragraphs

Chronic systemic disease infectious metabolic or neoplastic may prevent the onset of menstruation just as it may produce secondary amenorrhea in later life and any such condition must be carefully searched for Last but by no means least among the etiological possibilities for late onset of the menarche are emotional and environmental factors which in this sensitive psychosexual area may be subtle and difficult to identify Intolerable conscious or subconscious personal and environmental conflicts may have their somatic manifestation in a repudiation of sexuality as such and menstruation is certainly one of the most obvious manifestations of the femaleness which is being repudiated The hormonal physiology of menstruation is so delicate and cortical hypothalamic hypophyseal ovarian endometrial relationships so intimate and complex that a stimulus initiated in the cortex may well find its response in endometrial inactivity

Should no local or systemic abnormalities be found and the patient deemed to be in a reasonably stable emotional state (which in an adolescent permits considerable latitude!) the patient and her mother should be reassured concerning her menstrual status with the information that (1) this is a not infrequent and normal physiological variant and (2) the late onset of the menarche in no way compromises reproductive function in the future She should be told that after all the only physiological usefulness for the menstrual cycle is a preparation for reproduction and that since she does not under ordinary circumstances wish to reproduce at this age menstruation is actually physiologically unnecessary for her

It may be psychologically necessary however because the girl may have a not unreasonable feeling of being an abnormal person unless she menstruates the way her contemporaries do Furthermore for some unknown reason the mother of such a child is frequently most insistent that some effort be made to bring on the menarche and no amount of rational explanation will overcome this emotional fixation

Under these circumstances there is no reason why a few artificial menstrual cycles produced by exogenous estrogen should not be used as a valid therapeutic procedure This may be carried out by the administration of 3 to 5 mg of diethylstilbestrol daily by mouth for 20 days following which a period of estrogen withdrawal bleeding will occur within five to ten days thus convincing the patient and her mother that she can in fact menstruate This may be repeated for two or three cycles followed by a period of therapeutic rest to find whether or not this artificial hormonal stimulus has in some way triggered the patient's hormonal mechanism so that cyclic menstruation results Should the latter not occur a few induced periods per year should not be harmful but prolonged and excessive administration during teenage years especially should be avoided because such therapy depresses pituitary gonadotrophin activity The spontaneous onset of normal menstruation has certainly been known to occur as late as the eighteenth or nineteenth year and excessive previous hormone therapy may only further delay the already delayed maturity

Diethylstilbestrol occasionally produces nausea and even vomiting in which case some other orally administered estrogen may be used The reason for using stilbestrol first is that this synthetic compound is much less expensive than natural estrogens but if it is found desirable to use the latter conjugated equine estrogens in amounts of 3 75 mg daily for 20 days may be used ethinyl estradiol in amounts of 05 mg is also satisfactory These substances are administered orally

It must be remembered that this type of therapy does not stimulate the ovary It is in fact a replacement for ovarian function It not only does not produce but actually depresses ovulation and may well depress ovarian hormone production also Therefore the main function of this therapy is really a psychological one *i e* to present to

such is actually the menopause Therefore when the cessation of menstruation occurs physiologically because of primary ovarian failure at the conventional menopausal age therapy is rarely necessary (see subsequent paragraphs) On the other hand there are unusual and as yet but little understood cases of primary ovarian failure in younger women The expression "menopause praecox or premature menopause has been conventionally and incorrectly used for many years to describe and identify secondary amenorrhea whatever the cause in young women This expression should be used only for those patients who have been proved to have acquired primary ovarian failure before the age of forty To qualify for such a diagnosis a young woman must fulfill the following requirements (1) secondary amenorrhea (2) consistently high FSH excretion at menopause levels (3) vaginal smear or endometrial biopsy showing no estrogenic activity (4) actually observed ovaries (either by culdoscopy or laparotomy) which are atrophic and senile in appearance Patients of this type usually appear with a chief complaint of secondary amenorrhea fairly severe hot flushes and various subjective symptoms such as depression nervousness loss of libido etc The cause of this extraordinary premature ovarian senility is completely unknown and fortunately the condition is not common No satisfactory treatment of this condition exists at the present time except substitution therapy with estrogen in the minimal amount which will relieve the patient of distressing symptoms Stilbestrol 0 2 to 0 5 mg per day is usually sufficient for this purpose As has been mentioned complete or partial cessation of ovarian function may be due to a cessation of gonadotrophic stimulus from the pituitary Although the symptoms of this type of indirect ovarian failure may be somewhat the same the treatment is quite different and therefore it is important to identify this kind of case Gonadotrophin activity of the pituitary may be determined by the examination of a twenty four hour urine specimen for FSH content This test is done by most adequately equipped biological laboratories and may be considered more accurate and satisfactory than most other biological assays FSH output by the pituitary under normally functioning hormonal conditions varies from a few mouse units to 30 or 40 Excessive excretion of FSH of over 100 mouse units per twenty four hour specimen is generally considered to be a menopausal level because it indicates that the hypophysis is free from any estrogenic inhibiting effect Under ordinary circumstances the amount of estrogen secreted by the normal ovary inhibits gonadotrophin secretion by the pituitary gland The continued complete absence of FSH excretion indicates the presence of either some definite pituitary pathology or some unsuspected psychiatric factor inhibiting hypothalamic pituitary stimulation Thus the treatment of this type of patient rests not in attempts to provide ovarian steroid substitution therapy but in attempts to identify and treat the pituitary pathology which has resulted in gonadotrophin failure Occasional cases of chromophobe adenomas of the pituitary for instance develop amenorrhea as the first clinical symptom

Not infrequently cases of partial pituitary ovarian failure are seen which are represented by menstrual irregularities and occasional anovulation Partial ovarian failure is represented hormonally either by variations in the amount of ovarian steroid excreted or by variations in cyclic function Again for the most part the clinical evidence of these ovarian aberrations is a change in menstrual function varying from amenorrhea to menometrorrhagia It is quite apparent that in order to produce estrogen during the first two weeks of the menstrual cycle and estrogen plus progesterone during the latter two weeks the ovary must go through a process of ovulation at about the middle of a twenty-eight day cycle (Actually regardless of the length of the menstrual cycle ovulation if it occurs at all almost always occurs fourteen days before the next expected period) If ovulation does not occur no corpus luteum is formed by the ruptured graafian follicle and no progesterone is produced Cyclic bleeding may occur however even in the absence of ovulation this is known as anovulatory bleeding or anovulatory menstruation Since in the absence of progesterone no progestational changes occur in the endometrium bleeding develops from endometrium of a purely proliferative (estrogenic) type and although this type of menstrual bleeding may be clinically indistinguishable from the bleeding which occurs from progestational or secretory endometrium it not infrequently is abnormal in amount and the period itself may be unduly prolonged

The anovulatory cycle is identified by premenstrual curettage or endometrial biopsy and need not be treated unless the patient is an infertility problem or menstruation is so profuse or prolonged that

Table 1 The Characteristic Hormonal Abnormalities in Cases of Amenorrhea (Assuming that Local Systemic or Psychiatric Causes Have Been Eliminated)

	GONADOTROPHINS	ESTROGENS	ENDOMETRIUM	OVARY	17 KS
Pituitary inadequacy	0	0	Atrophic	Inactive	Normal or low
Primary ovarian failure (ovarian agenesis or menopause)	++++	0	Atrophic	Atrophic	Normal
Endometrial failure (rare)	+ or ++	++++	None	Normal	Normal
Hyperhormonal amenorrhea	+ or ++	++++	Hyperplastic	Normal with no corpora lutea	Normal
Polycystic ovary	? or + or ++++	Variable	Variable	Multiple follicular cysts	Normal
Adrenal cortical hyperplasia or tumor	+	Minimal	Variable	Atrophic Grossly normal Polycystic	Elevated
Thyroid disease	+	Minimal	Variable	Normal	Low in myxedema

dentally with amenorrhea for instance nor does it emphasize enough the fact that either no menstruation or profuse menstruation may have the same etiological factors With limitations like these in mind however they may be used as a satisfactory framework for the identification of organic or psychiatric pathology other than hormonal

If the investigator has proved to his own satisfaction that none of the conditions cited exists in the patient who complains of one of these symptoms he may then assume that the hormonal function of the ovary is unsatisfactory either because the ovary is incapable of producing its appropriate steroids estrogen and progesterone or that it is not being properly stimulated to do so by gonadotrophins from the pituitary With these possibilities in mind the investigation of the hormonal causes of dysmenstruation becomes somewhat easier Table 1 may help to explain the technique by which any of these abnormalities should be investigated An attempt has been made to provide means of identification for all the gradations of ovarian activity from ovarian agenesis (and therefore no activity) to normal ovulation (and therefore normal cyclic ovarian function) This diagnostic process of seeking to identify accuse and convict the guilty gland involves certain specific tests for further information concerning which the reader is referred to the monograph by Escamilla

THERAPY OF INADEQUATE HORMONAL FUNCTION OF THE OVARY

The therapy of inadequate ovarian hormonal function depends not only on the degree of hormonal failure but also on the therapeutic objective which the physician desires to obtain for his patient Although not a luxury certainly menstruation is not a necessity except in the infertility patient therefore except in the treatment of infertility and possibly in rare psychological situations a patient need not be treated purely for the purpose of recreating menstrual cycles On the other hand certain patients who show other evidence of estrogen deficiency such as loss of other secondary sex characteristics certainly need and deserve either substitution or stimulative therapy

The patient with ovarian agenesis (or more properly gonadal dysgenesis) for instance should be given exogenous estrogen therapy not to make her menstruate but to provide her with the secondary sex characteristics which will transform her from a sexually completely undeveloped individual into a synthetic female Once this type of congenital abnormality is recognized the therapy consists of cyclic estrogen administration Five mg of diethylstilbestrol is administered daily for three weeks A decreasing dosage is resumed at the onset of withdrawal bleeding which usually occurs five to ten days following the interruption of therapy A gradual decrease in dosage is then continued until a minimum level is reached which will develop and maintain the patient s secondary sex characteristics Estrogen administration may be continued indefinitely in this fashion If the patient is nauseated by stilbestrol other oral estrogens as previously described may be administered

The ovary which is present but nonfunctional presents a somewhat different therapeutic problem Primary ovarian failure as

The Menopause

Since the menopause is the clinical manifestation of the cessation of ovarian function it is appropriate that this physiological condition be considered in the section on the female gonad It is important to remember however that the menopause is a *physiological* and *not* a *pathological* phenomenon It is not a disease but a normal representation of normal *primary ovarian failure* Menstruation ceases for various other reasons at various other times of life but in middle age when the ovary becomes senile and atrophic and ceases to respond to gonadotrophic stimulation it will no longer fulfill its two basic functions of egg and sex hormone production At this time the woman experiences irrevocable evidence of the process of aging The human female is probably the only menstruating primate who ceases to menstruate at about middle age This might be considered a sign of evolutionary progress because it is possibly unwise genetically emotionally and physiologically for the human female to produce offspring after middle age Therefore since the menstrual process is no longer useful nature has provided a technique whereby it ceases

Sometime between the ages of forty and fifty five the ovary undergoes gradual or rapid regressive atrophy which results in a great variety of clinical changes mostly represented by gradually diminishing menstrual function In some cases there is a gradual decline in estrogen production over a fairly long time—in fact possibly as long as two or three years In others the ovaries cease this activity quite abruptly thus a woman who has had very adequate estrogen production may very quickly within a period of a month or two experience practically complete cessation of ovarian function In some women the ovaries may revitalize themselves periodically their activity may almost cease only to recur briefly in declining amounts until after a year or two no evidence of further estrogen production can be found

The menopause as such then may occur fairly suddenly or it may drag itself out over a period of a year or more Ultimately however not only are no more eggs produced but so far as we know there is very little if any sex hormone production No amount of gonadotrophin stimulation can produce activity in the menopausal ovary and even though the hypophysis secretes large amounts of gonadotrophin postmenopausally—in fact because it is released from estrogen depressive action possibly more even than during actual menstrual life—the ovary does not use it and it is excreted in large amounts in the urine Measurement of gonadotrophin in the urine is one of the methods of diagnosing the physiological condition of the menopause when it is important to differentiate it from possible pathological amenorrhea

There is considerable controversy at the present time concerning the activity of the postmenopausal ovary Certain investigators believe that the postmenopausal ovary continues to carry out some kind of hormonal function albeit at a much more modest level than during active menstrual life and there is some evidence that this may possibly be true in some women On the other hand it is extremely difficult to demonstrate physiologically any evidence of estrogen production by the postmenopausal ovary The psychological implications of the menopause and of surgical castration by oophorectomy are so profound in the human female that subjective evidence of ovarian function postmenopausally or postcastration is most undependable Objective evidence of minimal estrogen production may be obtained by observation of the vaginal smear or possibly of endometrium obtained from endometrial biopsy but even if evidence of minimal estrogen activity is present it is not proof that the postmenopausal ovary is the source of this steroid because estrogen is not only produced by the adrenal but is also ingested in various amounts from various different kinds of food Even potato contains estrogenic substance and at the present time meat and poultry are likely to contain synthetic estrogenic substances as a residue from estrogen administration to cattle and poultry for the purpose of tenderizing meat and producing hormonal caponization

What however are the clinical symptoms of this process of ovarian aging when the rest of the woman may be active healthy and vital physically emotionally and mentally? So far as we know at the present time the only symptoms which have actually been proved to occur as a result of sudden or possibly even gradual ovarian deficiency are the symptoms of vasomotor instability such as *hot flushes* and possibly transitory dizziness and headaches

These in addition to the *amenorrhea* which has provided this condition *with its* name are the only *symptoms which in* any way have been *proved to result* from estrogen depletion An extraordinary *num*

some kind of therapy is considered advisable. In the latter case proliferative endometrium may be changed to a progestational or secretory variety during the latter two weeks of the cycle by the administration of progesterone or progesterone-like compounds. By thus developing a mature premenstrual endometrium and permitting bleeding to occur from it, normal menstruation results, and the patient is relieved of the profuse and prolonged blood loss which previously occurred. Until recently the most satisfactory technique of progesterone therapy was the intramuscular injection of 10 mg. of progesterone daily for about ten days. There are now available, however, synthetic progesterone-like steroids commonly called 19 Nor compounds which produce striking progestational effects when administered by mouth. The dosage of these substances has not as yet been accurately worked out, but they also are administered for about ten days premenstrually in order to produce a satisfactory secretory endometrium.

The anovulatory cycle in the infertility patient is quite another problem because the absence of ovum production, not the menstrual abnormality, is the critical factor. Since anovulation very probably represents inadequate or aberrant pituitary-ovarian relationships, the theoretical treatment of anovulation should be administration of the appropriate gonadotrophin. At the present time, however, this is impossible for two reasons. The first is that there is still considerable ignorance concerning the exact type and amount of gonadotrophin (or gonadotrophins) which is (are) secreted at various times in the menstrual cycle, and the second is that no gonadotrophin is available therapeutically which has the characteristic of stimulating the primate ovary to ovulation. Hopeful advances in this direction have been made by VanWagenen and Simpson, who have produced numerous ovulations in the primate (Rhesus) by the administration of Rhesus pituitary extracts. Such is the species specificity of gonadotrophin that it is hoped that, whereas equine, bovine or sheep pituitary extracts have failed to stimulate the human pituitary in the past, possibly primate pituitary extracts will have a more satisfactory effect in the future.

Much has been written concerning the use of so-called therapeutic radiation of the anovulatory ovary in attempts to produce ovulation. There is reasonably good evidence that ovarian irradiation (in amounts of about 200 r over the pelvis) has some effect on the ovary which occasionally causes it to ovulate. Whether this radiation produces a depression of an inhibitory substance (estrogen?) on hypophyseal gonadotrophin secretion or whether its action is mediated otherwise is unknown. It must be emphasized, however, *that this type of therapy has great genetic* danger because of the possibility of producing chromosomal mutations which may result in genetic abnormalities in subsequent generations. Therapy of this type is therefore considered inadvisable.

The cyclic nature of menstruation with its ebb and flow of gonadotrophin and ovarian steroids is such that any hormonal imbalance may alter not only menstrual function but also the actual physiological condition of the ovary. Occasionally, as a result of causes unknown, cyclic function ceases and the ovary, as though freed from some governing influence, persistently and continuously secretes estrogen without any tidal variation in amount or unaccompanied by progesterone production. This results in estrogenic hyperplasia of the endometrium with a temporary period of amenorrhea followed by profuse and severe endometrial bleeding. Such a condition is identified by curettage, which also occasionally has a therapeutic effect, but under these circumstances the same sort of progestational therapy as previously mentioned for the anovulatory cycle should be carried out.

Another type of cyclic malfunction, probably again due to some dislocation of pituitary-ovarian hormonal relationships, is the development of the polycystic ovary. This condition produces amenorrhea and is not infrequently accompanied by obesity and hirsutism; therefore great care must be taken to differentiate this condition from adrenal cortical hyperplasia or the presence of a functioning adrenal tumor (*q.v.*). Bilateral polycystic ovaries are usually identifiable on pelvic examination because this type of ovary is two or three times normal size, but it is sometimes advisable to carry out culdoscopy to verify this diagnosis. The only cure for this condition known at the present time is bilateral ovarian wedge resection accomplishing the removal of about one third of each ovary. The percentage of cures following such a procedure with subsequent ovulation and normal menstruation is surprisingly high, being somewhere in the region of 80 per cent. The reason why such a surgical procedure cures this condition so often is at present unknown.

estrogen replacement until the age when the menopause would probably be expected

Viewing the menopause from this stand point then how can we most efficiently and successfully care for the patients who consult us for advice and help during this time of life? Again it must be stressed that no kind of therapy should be undertaken until a thorough investigation is made by history physical examination and neces sary laboratory work If no organic disease is found it may be said that therapy could be divided into three categories psycho logical hormonal and medical

It is hoped that the foregoing discussion has sufficiently emphasized the fact that many symptoms attributed to the meno pause are actually due to the psychological stresses which occur at this time of life Frequently these stresses involving ad justments to physical status environment family and friends are due to inadequate knowledge and understanding of the physi ological process through which the patient is going Because there are such common lay misconceptions concerning the meno pause it is frequently necessary not only to disabuse patients of strange and bizarre ideas but also to educate them Emphasis on the naturalness and innocuous charac teristics of the menopause is frequently of considerable help for patients who are confused The simple psychotherapy of dissemination of knowledge with sympa thetic understanding should always be ade quate for helping patients through this time of life Occasionally however pro found depression accompanies the meno pause in the form of involutional melan cholia or even paranoid states These pa tients have almost always had a previous history of psychiatric instability which the additional strain of the climacteric brings into focus They are therefore more psychi atric problems than menopausal and should be placed under psychiatric care

Nonspecific medical therapy for the menopause should be carried out before resorting to the tempting expedient of using estrogen substitution therapy Mild bar biturate administration greatly helps a patient in her necessary readjustment to herself and to her environment The recent surge of enthusiasm for "tranquilizing drugs has resulted in a complete new ap pendix to our pharmacopoeia Undoubtedly many of these are worthwhile in ameliorat ing the psychological problems arising at this time of life and their judicious and careful use may be of great assistance to the physician The type and amount of tranquilizing drug must depend on the resourceulness and experience of the physi cian but it is quite apparent that what may be a most satisfactory type of therapy in one patient is not adapted to another nor are these medications a substitute for helping the patient to achieve what might be called endogenous rather than exoge nous tranquility and equanimity

In the event that medical therapy has been unsuccessful especially in the relief of hot flushes produced by vasomotor in stability hormonal therapy for the meno pause is legitimate and necessary It must be remembered however that aside from the cessation of menstruation vasomotor instability is actually the only immediately recognizable change in this physiological process Therefore hormonal substitution therapy should not be engaged in unless the patient s symptoms are thought to re sult from this vascular change There are many types and varieties of available estro gen both naturally occurring and syn thetic Whereas conjugated natural estro gen was at one time almost universally administered by intramuscular injection this somewhat inconvenient and expensive mode of estrogen therapy is now entirely unnecessary because numerous synthetic and naturally occurring estrogens are ade quately potent when administered by mouth The writer can think of no situa tion in which it would be medically advis able to administer estrogen by injection rather than orally The administration of 0 1 mg to 0 3 mg of diethylstilbestrol daily for the relief of hot flushes should certainly be adequate for estrogen replace ment therapy This medication is preferred because it is so inexpensive but if by any chance it produces nausea and vomiting which it does rarely natural estrogen ad ministered by mouth may be substituted in the form of ethinylestradiol in the dosage of 0 05 mg or sodium estrone sulfate in amounts of 0 625 mg per day So far as any physiological measurements of estro genic activity are concerned there is no identifiable difference in the estrogenic activities of the natural and the synthetic compounds

It must be remembered that hormone therapy at the time of the menopause since it is replacement therapy actually only postpones the inevitable process of estrogen depletion which every menopausal woman must go through The rationale for therapy at this time therefore is not to give com plete replacement and thereby postpone the inevitable but so gradually to decrease the

ber of other symptoms have been attributed to ovarian failure simply because women occasionally at this time of life have complained of them Excitability weeping palpitation depression fatigue irritability constipation dyspnea sweating and insomnia are but a few of the symptoms for which the menopause is blamed but there has never been any proof whatever that the menopause *per se* or estrogen depletion is responsible for any of this extraordinary galaxy There is no question that these symptoms *do* occasionally occur at this time of life and therefore if we do not accuse the menopause as the etiological factor to what may we attribute their origin? If we can answer this we may obtain some appropriate focal point for therapy There are possibly two sources of these symptoms on which it is worthwhile to comment

We must be constantly aware of the fact that symptoms of which women complain at this time of life and which are so commonly attributed to the menopause may not actually be symptoms of the menopause at all but of concomitant unrecognized pathological conditions This is the age during which common degenerative diseases begin to manifest themselves and symptoms of these diseases may be parading in the guise of menopausal symptoms while the real etiological factor is lurking in the background Women suffering from hypertension diabetes hyperthyrodism even brain tumors and many other common or bizarre diseases the symptoms of which have simulated exactly those frequently attributed to the menopause are all too frequently treated by estrogen substitution therapy because they are erroneously thought to be suffering from ovarian failure It is therefore extremely important to investigate every patient during this stage of life who has incidentally ceased to menstruate in order to avoid the misfortune of later being presented with irrevocable evidence of a full blown degenerative disease the process of which might have been retarded had it been recognized earlier

The other possible source of the many symptoms described above is of course the psychological change which occurs at this time of life and which the menopause brings into focus The menopause is the irrevocable physical expression of the process of aging It brings irresistibly to a woman s mind that she has fulfilled her reproductive physiological usefulness that she is no longer young and that she must readjust her approach to life A frequent topic since Old Testament times the involutional psychoses of the menopause are today a favorite item for psychiatrists and specialists in psychosomatic medicine Individuals acquire somatic symptoms because of the attitudes toward the menopause which their education and background and emotional life have led them to develop It is a time of life when psychological stability is frequently difficult to sustain and women in these decades develop unnecessary fears and apprehensions concerning themselves their environment and their relationship to their families and friends Add to these factors the additional folklore and gossip concerning the alleged misfortunes of the menopause and it is really not surprising that women suffer from all sorts of subjective complaints at this time of life It is quite apparent that the unfortunate symptoms must be treated but it is also quite apparent that they must be treated by techniques other than estrogen replacement as a substitute for ovarian activity This type of therapy is only a postponement of the inevitable

This is not to deny completely the fact that there are other pathological changes which occur as a result of estrogen deficiency especially in women who have been deprived of estrogen surgically or by radiation in early age The possibility that cessation of estrogen production may be an etiological factor in osteoporosis—but certainly not the primary one—is worthy of consideration Osteoporosis is part of the process of aging but it is undoubtedly aided and abetted by loss of estrogen We must remember however that this condition occurs in males and also what is probably most important that it is impossible to reverse this process by later administration of estrogen even though a patient may be put into positive calcium balance by estrogen It is possible that osteoporosis may occur in women who receive exogenous postmenopausal estrogen throughout their postmenopausal years The occurrence of osteoporosis however in a young woman who has been deprived of ovarian function either surgically or radiologically is an entirely different matter This woman really has physiological need of estrogen because of the pathological deprivation of this hormone at an age when it is supposed to be physiologically present Therefore in order to reproduce the characteristics of this age group in terms of estrogen production it is most certainly advisable to carry out

DISEASES OF THE THYMUS GLAND

Many possible functions have been attributed to the thymus gland but thus far none has been subject to proof Classic extirpation experiments in a variety of animals have given no conclusive results Extracts of many types have been tested but the results have been variable The planning of such experiments is exceedingly difficult because of the fact that in our ignorance of the functions of the thymus the conditions for making any effects recognizable have not been fulfilled There are certain clinical relationships which suggest that the thymus has an endocrine function Myasthenia gravis is associated in many instances with a tumor of the thymus In many cases of hyperthyroidism a disease associated with thymic enlargement muscular weakness is a prominent feature and the occasional development of myasthenia gravis in association with exophthalmic goiter is probably more than coincidental In a number of reported cases a thymoma has been associated with depressed erythrogenesis and anemia relieved following thymectomy Much discussion has taken place about the relationship of thymus enlargement to sudden death in infants particularly during anesthesia The function of this organ and its relationships to clinical disease are still for the most part shrouded in mystery

Anatomy and Physiology In the normal thymus of infants there is a well defined cortex consisting of closely packed masses of cells (thymocytes") resembling lymphocytes and a medulla During the process of differentiation into cortex and medulla concentric masses of cells the Hassall corpuscles appear in the sheets of epithelial cells of the medulla Opinion varies as to the nature of the thymocytes Some observers contend that the thymocytes are in reality lymphocytes and appear in the gland only after invasion from without Others believe that the morphologic similarity does not establish their common identity and feel that the cell is formed *in situ* from thymic epithelium

Near the age of puberty the gland becomes narrower and occupies a relatively smaller portion of the anterior mediastinum although in actual size it may be larger than in the infant As involution takes place thymic tissue is replaced by adipose tissue which separates the lobules from each other The number of lymphocytes in the cortex and medulla decreases but in spite of these changes thymic tissue can with rare exceptions be found in any person regardless of age type of illness or cause of death There may be an acceleration of involution brought on by illness a so called accidental involution This is probably mediated by the increased adrenal activity in response to stress

Animal experiments have demonstrated relationships of the thymus to certain of the endocrine glands Castration and administration of thyroxin in rats cause comparable increases in the weights of the thymus the lymph nodes and the spleen Thyroidectomy and treatment with testosterone tend to decrease the weights of these structures These procedures also prevent the increase in weight of the thymus which follows castration There is a reciprocal relationship between the size of the adrenal cortex and the thymus Deficient adrenal cortical secretion results in hypertrophy and the injection of adrenocortical steroids or the adrenotrophic hormone of the pituitary results in a decrease in thymic weight Rats exposed to low atmospheric pressures for more than two days exhibit an increase in adrenal weight and a significant decrease in the weight of the thymus and testes

Evidence has been obtained by some investigators of a neuromuscular blocking effect in extracts of thymus and pancreas while others have concluded that extracts of thymus from patients with myasthenia gravis are capable of inhibiting acetylcholine synthesis in contrast to similar preparations from normal individuals No firm conclusions can be drawn from any of these observations

Pathology *Atrophy* Nutritional atrophy is a common finding since the thymus involutes rapidly during inanition and febrile illnesses which last for more than a few days Nine days of starvation in the rabbit

amount of available estrogen that the patient is eased into a state of complete estrogen depletion rather than suddenly thrust into it We see no necessity for continued estrogen administration over a period of years as is so often practiced and advocated elsewhere It may be asked why this continued use of exogenous estrogen should not be carried out if the patient so desires and if she thinks it makes her feel better There are two answers to this question One is the possibility of carcinogenesis as a result of prolonged and indiscriminate estrogen therapy and the other is the simple fact that it is not a physiological necessity

That estrogens are carcinogenic in the human female has not as yet been proved Suspicion has been cast upon this steroid as being a factor not only in uterine and cervical carcinoma but also in mammary carcinoma Its contribution to carcinogenesis is still speculative Possibly the most incriminating evidence concerns carcinoma of the endometrium it has been shown that prolonged uninhibited estrogen production produces a condition of adenomatous hyperplasia which seems almost imperceptibly to pass through an innocuous zone into the area of malignant metaplasia Therefore although the status of estrogen as a carcinogenic steroid is at present unclarified it is nevertheless under suspicion and if it is unnecessary to use this drug are we therefore because of this suspicion justified in using it?

The other reason for not using this drug following the menopause is admittedly a somewhat philosophical one Nature has arranged matters so that the human female does not need estrogen after the menopause to maintain her mental or physical health well being and vitality Prolonged estrogen administration therefore becomes a specious attempt to turn back the clock and to assist the patient in escape from reality Life from the beginning is a process of aging and one aspect of happiness is a mature realization of and acceptance of this fact If we as physicians aid and abet an escape from reality by trying to help women think they are young when they really aren t are we actually contributing to their welfare? It is incumbent upon us in every specialty therefore to *treat* this condition known as the menopause but let us remember that hormonal replacement therapy is one of the minor and temporary aspects of this treatment

C LEE BUXTON

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certain instances of sudden death there is no justification for the belief that radio therapy or extirpation of the thymus would have prevented death Coe described eight thymic deaths in 2500 operations in children less than eighteen months of age They were not due to anesthesia or to obstruction of the respiratory tract The outstanding characteristic was complete absence of respiratory effort and ordinary methods of resuscitation were not beneficial The heart continued to beat normally after respiration had ceased He suggested that some curare like substance might be released under these conditions an interesting suggestion in view of the possible relationship of the thymus to myasthenia gravis

The Thymus and Respiratory Obstruction Chronic stridor attacks of cyanosis and choking in infancy have often been attributed to the thymus With modern diagnostic methods these symptoms are usually shown to be the result of other causes such as congenital hypotonia of the larynx congenital obstructive anomalies of the respiratory tract inflammatory lesions tetany and other local or general conditions At the age of six months both the body and the thymus have doubled in weight The body has tripled in weight by the end of the first year the thymus not until five years Thus after six months to one year the thymus becomes increasingly insignificant as a possible cause of respiratory obstruction Enlargement of the thymus in the anteroposterior plane is most apt to cause respiratory obstruction and careful roentgenograms in oblique as well as anteroposterior positions are necessary in evaluating it as a factor in any case Bronchoscopy may show compression and symptoms usually cease after radiation therapy The diagnosis cannot be made with any certainty by physical examination

Irradiation of the Thymus and Carcinoma of the Thyroid Irradiation of the mediastinal region in children is not without danger There is evidence to indicate a relationship between previous irradiation of the chest and the development of carcinoma of the thyroid It has been observed that one of every thirteen children with carcinoma of the thyroid has a history of previous irradiation and other studies show that six of every 1400 infants irradiated before fourteen months of age will develop thyroid carcinoma before the age of eighteen years

Relationship of the Thymus Gland to Myasthenia Gravis (See section on Myasthenia Gravis)

Treatment. The indications for *roentgen ray therapy* have changed in recent years Prophylactic" irradiation to prevent sudden death is not warranted and therapeutic irradiation for respiratory obstruction is indicated only after all other possible causes have been ruled out Many tumors of the thymus are sensitive to irradiation and remissions have been reported in myasthenia gravis following roentgen therapy On the whole however this form of treatment has not been satisfactory

Before treatment of a thymic neoplasm a biopsy should be performed for histological diagnosis Ideal treatment is *surgical removal of thymic tumors* along with the remainder of the gland Many authors believe that this should be followed by a full course of irradiation to the mediastinum as the distinction between benign and malignant tumors is difficult histologically as well as grossly In several reported cases of benign" tumors metastases developed two to three years postoperatively Early excision of all undiagnosed anterior mediastinal masses is advisable and all tumors originating in the thymic area should be regarded as potentially malignant

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will reduce the thymus to 10 per cent of its original size

Infections Metastatic abscess formation in the thymus during bacteremia is rare Tubercles are occasionally found in association with infection of the tracheobronchial nodes Gummas of the thymus have been reported occasionally

Neoplasms No group of tumors has proved more difficult to interpret and classify than those of the thymus gland The problems involved are those which have complicated the embryological and histological study of the gland Because of this lack of specific knowledge of the true histogenesis of the constituents of normal thymus the generic term thymoma has come into use indicating only the primary source of a new growth from thymic parenchyma A thymoma may originate from thymic lymphocytes reticular cells Hassall s bodies or the thymic stroma Norris feels that the thymomas often associated with cases of myasthenia gravis should be regarded as adenomas produced by an extreme degree of local hyperplasia of the thymic epithelium

The thymoma is a slowly growing tumor which may arise from both the thymocytic and epithelial cells The relative proportion of these cellular types varies greatly both in different tumors and in various regions of the same neoplasm Features commonly present are dense fibrous capsule distinct fibrous trabeculae the palisading of epithelial cells about cystic spaces foci of necrosis cyst formation and calcification Most of these tumors lie anterior to the aortic arch and base of the heart but may be located lower They are usually round or oval clearly differentiated from the remainder of the gland and may contain sufficient calcium to be seen radiologically Tumors of the thymus are usually encapsulated but may be adherent to the surrounding organs and invade the pericardium pleura or lungs Distant metastasis is rare The association of a thymoma and agenesis of erythrocytes has been reported in fourteen instances Myasthenia gravis has been present in only two of these cases Typically the bone marrow study revealed few or no erythrocyte precursors and myelopoiesis and megakaryocyte activity were usually normal Thymectomy apparently resulted in relief of anemia in two cases Improvement in two and failure in two There seems to be a definite relation between suppression of the erythrogenesis and the presence of a thymoma in these cases

Myasthenia gravis develops in many patients with benign thymomas In several instances this disease has appeared a few years after removal of the tumor Carcinoma of the thymus a malignant tumor which metastasizes widely is almost never associated with myasthenia gravis

Clinical Diagnosis of Thymus Enlargement Neoplastic enlargement of the thymus of considerable size may occur without the production of any local signs and symptoms If the enlargement is in the anteroposterior diameter cough and hoarseness pain in the chest and neck dysphagia and compression of the large veins may develop Pleural and pulmonary involvement with hydrothorax may occur and extension through the chest wall has been described

Other conditions which must be considered in differential diagnosis are tracheobronchial lymphadenitis mediastinal pleurisy paravertebral abscess aneurysm of the aorta and other mediastinal neoplasms

In the roentgenogram the shadow is more or less circular sharply defined and located just above the cardiac shadow Lateral films will show that it occupies the anterior mediastinum In advanced cases with extension to the pleura and lungs a circumscribed shadow may not be visible Other types of mediastinal tumor are likely to be found higher and may occupy the middle and posterior portions of the mediastinum It is difficult at times to differentiate between a thymoma and an aortic aneurysm

Because of the great variation in size of the organ in relation to age physical condition and other factors there is no satisfactory way of diagnosing diffuse enlargement of the thymus Some of the tumors are so small that they are not recognized before operation or autopsy and then only by careful search However with use of the lateral exposure and tomography most thymic tumors can be discovered by the roentgenologist

Diseases of the Thymus in Infants and Children *Status Thymolymphaticus* Most of the evidence at present indicates that the state of the thymus and lymphatic structures originally described as enlarged and as associated with the syndrome known as "lymphatic constitution" or status thymolymphaticus is in most instances within the limits seen in normally developed persons who have died of a variety of causes In many of the cases described at autopsy there is adrenal atrophy which is known to be associated with enlargement of the thymus If such a condition as status thymolymphaticus exists and if it is related to

certain instances of sudden death there is no justification for the belief that radio therapy or extirpation of the thymus would have prevented death Coe described eight thymic deaths in 2500 operations in children less than eighteen months of age They were not due to anesthesia or to obstruction of the respiratory tract The outstanding characteristic was complete absence of respiratory effort and ordinary methods of resuscitation were not beneficial The heart continued to beat normally after respiration had ceased He suggested that some curare like substance might be released under these conditions an interesting suggestion in view of the possible relationship of the thymus to myasthenia gravis

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